FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLET OF OXYBUTYNIN HYDROCHLORIDE

Dissertation

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THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY
In
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By

26101011

Under the Guidance of

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All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that **26101011** carried out the dissertation work on **"FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLET OF OXYBUTYNIN HYDROCHLORIDE"** for the award of degree of **MASTER OF PHARMACY IN PHARMACEUTICS** of **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI** and is bonafide record work done by him under my Supervision and Guidance in the Department of Pharmaceutics, C. L. Baid Metha college of Pharmacy, Chennai-600 097 during the academic year 2011-2012.

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DECLARATION

I do hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLET OF OXYBUTYNIN HYDROCHLORIDE"** by **Reg. No: 26101011** submitted in partial fulfillment for degree of **Master of Pharmacy in Pharmaceutics** was carried out at C.L.Baid Metha college of Pharmacy Chennai-97 under the guidance and supervision of DR**. R.KUMARAVELRAJAN M. Pharm., Ph.D during** the academic year 2011-2012. The work embodied in this thesis is original, and is not submitted in part or full for any other degree of this or any other University.

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ABBREVATIONS

HCl – Hydrochloric acid

HPMC-Hydroxypropyl Methyl cellulose

MCC-Microcrystalline Cellulose

IPA-Isopropyl alcohol

ER-Extended Release

SR- sustained Release

IR-immediate Release

BP-British Pharmacopoeia

USP- United States Pharmacopoeia

FTIR- Fourier Transform Infrared spectroscopy

U.V-Ultra Violet spectroscopy

Std-Standard

Spl-Sample

GIT- Gastro Intestinal Tract

gm- Gram

mL- Milliliters

mm- Millimeters

Cm- Centimeters

BD- Bulk Density

TD- Tapped Density

CI- Carr's Index

HR- Hausner's Ratio

KP- Kilo Pounds

% RH- Percentage Relative humidity

SD- Standard Deviation

RPM- Revolutions Per minute

f_1- Difference Factor

f_2- Similarity Factor

Chapter 1

Introduction

Extended release drug therapy

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and injectables. Even today these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue[1].

The term controlled/extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue.

The oral route of administration for extended release systems has received greater attention because of more flexibility in dosage form design. The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Extended release [2]denotes that the system is able to provide some actual therapeutic control whether be it of temporal or spatial nature or both. In other words, the system attempts to provide a constant drug concentration in the target

tissue. It is this nature of this system that makes it different from sustained release systems.

1.1 Advantages of extended release dosage form: [3]

- **Improved patient compliance** and convenience due to less frequent drug administration.
- **Reduction in fluctuation** in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- **Increased safety margin** of high potency drugs due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care costs** through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- **Sustained blood levels**; the size and frequency of dosing are determined by the pharmacokinetic and pharmacodynamic property of drug. The use of extended release products may maintain therapeutic concentration over prolonged period.
- **Attenuation of adverse effect**, the use of extended release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, haemodynamic changes etc.

1.2 Disadvantages of extended release dosage for: [3]

- Toxicity due to dose dumping.
- Increased cost.

- Unpredictable and often poor *in vitro*- in vivo correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

1.3 Ideal candidate for extended/controlled release drug delivery systems: [4-6]

The desired biopharmaceutical characteristics of drugs to be used in the development of per oral controlled release dosage forms are:

Molecular weight	:	<1000 mg
Solubility	:	0.1mcg/ml
P^{ka}	:	>0.1% to 1% at pH 1 to 7.8
Apparent partition coefficient	**:**	0.5 to 2.0
General absorbability	:	From all GI segment
Stability	:	Stable in GI environment

Release should not be influenced by pH and enzymes.

Less protein binding.

To evaluate whether a drug is viable candidate or not for the design of per oral CR formulation, one must consider the following pharmacokinetic parameters of the drug.

Elimination half-life	:	Preferably between 0.5& 8 hours
Total body clearance	:	Should not be dose dependent
Elimination – rate constant	:	Required for the design
Absolute bioavailability	:	Should be 75% or more
Absorption rate	:	Must be greater than release rate

Therapeutic concentration :

The lower the c_{ss}^{av} and the smaller the v_d the lesser is the amount required.

Apparent volume of distribution (V_d):

The larger the v_d and Minimum Effective Concentration (MEC), the larger will be the dose size required. The maximum dose to be incorporated in to a per oral Controlled release (CR) formulations is about 500mg. The smaller the v_d , the easier is incorporation of drug in to dosage form.

Minimum toxic concentration (MTC):

MTC and MEC, the further apart these t values are, the safer the dosage and also suitable for drugs with very short $t^{1/2.}$

1.4 Unsuitable candidates for extended-Release dosage forms: [7]

- Short elimination biological half-life

  E.g. Penicillin G, Furosemide

- Long elimination biological half life (>12hr)

  E.g. Diazepam, Phenytoin

- Narrow therapeutic index

  E.g. Phenobarbital, Digitoxin.

- Not effectively absorbed in the lower intestine. E.g. Riboflavin, Ferrous salts.
- Large doses (>1g):

  E.g, Sulphonamides.

1.5 Controlled Release Formulations: [8]

1.5.1 Types of Controlled Release Systems

Matrix type tablets

- Hydrophobic & hydrophilic matrices.
- Plastic matrices
- Ion exchange resins
- Co-precipitates & solid dispersions.

Film-Coating Tablets

- Diffusion-controlled membrane
- Osmotic pumps
- Floating Tablets
- Swellable Tablets
- Mucoadhesive Tablets
- Complexation
- Cyclodextrins
- Pharmaceutical adhesives.

3) Multiple-Unit Tablets

II Capsules

1) Hard capsules
2) Soft elastic capsules
3) Floating capsules

III Micro granules/spheroids

IV Beads

V Pellets

VI Emulsions

VII Suspensions

VIII Liposomes

IX Micorparticles

X Nano particles

1.6 Matrix Systems*:* [9]

Definition:

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipient in order to achieve release by a continuous leaching of the drug from the inert matrix core.

1.6.1 Matrix Tablets:

These are the simplest & least expensive systems for controlled drug delivery. Their processing is reproducible & is similar to that conventional system. The polymer or other carrier is homogeneously mixed with drug.

Drug release from the bulk of matrix involves two matrix mechanisms:

1) The Erosion rate of the matrix determines the drug release state in matrices governed by erosion or dissolution

$$\left(\frac{dm}{dt}\right) = S\left(\frac{dx}{dt}\right)f(c) \qquad \text{eq (1)}$$

Where:

$\left(\frac{dm}{dt}\right)$ - Drug release rate.

S - Surface area

$\left(\frac{dx}{dt}\right)$ - Matrix erosion rate

$f(c)$ - Drug Concentration gradient

2) The diffusion through a barrier membrane describes drug release in insoluble coating via fick's second law of diffusion.

$$\left(\frac{dm}{dt}\right) = DSK\,\frac{(Cd - Cr)}{h} \qquad \text{eq (2)}$$

Where:

D – Diffusion coefficient

S – Exposed surface area

K –Partition coefficient

$(Cd - Cr)$ – Drug concentration gradient

1.6.2 Advantages of matrix system

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipments. Secondly, development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

1.6.3 Limitations of the matrix systems

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

1.6.4. Types of matrix systems

The matrix system can be divided into two categories depending on the types of retarding agent or polymeric materials.

1.6.4.1 Hydrophobic matrix system

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix

during drug release. As such, diffusion of active ingredient from the system is the release mechanism, and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic[9]. The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery become more important. Constant rate delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic.

1.6.4.2 Hydrophilic matrix system

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The presence of water decreases the glassy-rubbery temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain

favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix, Boniferoni *et al*. (1995) showed a relationship between rheological behavior of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs[10].

Swelling controlled release systems are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.

Drug release from swellable matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives recipients in the final formulation[9].

1.6.5 Materials used as Retardants in matrix Tablets: [11]

Various polymers have been investigated as drug retarding agents, each presenting a different approach to the matrix system. Based on the features of retarding polymer, matrix systems are usually classified into three main groups. They are:

Table: 1 Materials used as retardants in matrix Tablets

Nature of the polymer	Examples
Insoluble, Inert	Poly Ethylene, Polyvinylchloride, Ethyl cellulose and Methyl acrylate
Insoluble, Erodible	Carnaubawax, Stearyl alcohol ,Stearic acid PolyEthyleneglycol, and Triglycerides.
Hydrophilic	Methyl cellulose ,Hydroxy Ethyl cellulose Hydroxy propyl Methylcellulose, Xanthangum, Sodium alginate,and Chitosan.

1.6.6. Methods of preparation: [12]

Three methods may be used to disperse drug and additives in a retardant base.

❋ **Solvent evaporation technique**

In this technique a solution or dispersion of a drug and additive is incorporated into molten wax phase and the solvent is removed by evaporation.

❋ **Compression technique**

This involves the compression of granules, which may be prepared by wet granulation or dry granulation technique or direct compression of blend of drug, release retardant material and other additives.

❋ **Fusion technique**

Drug and additives are blended into the molten wax matrix at a temperature slightly above melting point more uniform dispersion can be obtained by this technique.

1.7 Drug Release from Matrix Systems

1.7.1. Mechanism of drug release from swelling controlled release systems

1.7.1.1 Polymer swelling and drug release

The overall drug release mechanism from swelling controlled release systems based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. When a matrix comes in contact with an aqueous solution, wetting occurs first at the surface and then progresses by way of microscopic pore spaces into the matrix. The excipient in the matrix also absorb water, hydrates and swells to block up the existing pores, dissolves the content to create a more porous structure, gels to form a more viscous solution giving rise to positive pressure opposing liquid entry or causes disintegration of the matrix . Before a liquid can enter a matrix, there must be a driving force, which is derived from the pressure difference. The rate of liquid penetration into the matrix is determined by balance of this force promoting fluid entry towards the interior and the viscous force opposing it, which soon develops as soluble excipients in matrix dissolve or swell[13]. The swelling of the matrix and consequent drug release by diffusion from the matrix and erosion of the matrix is shown in Figure 1a and 1b.

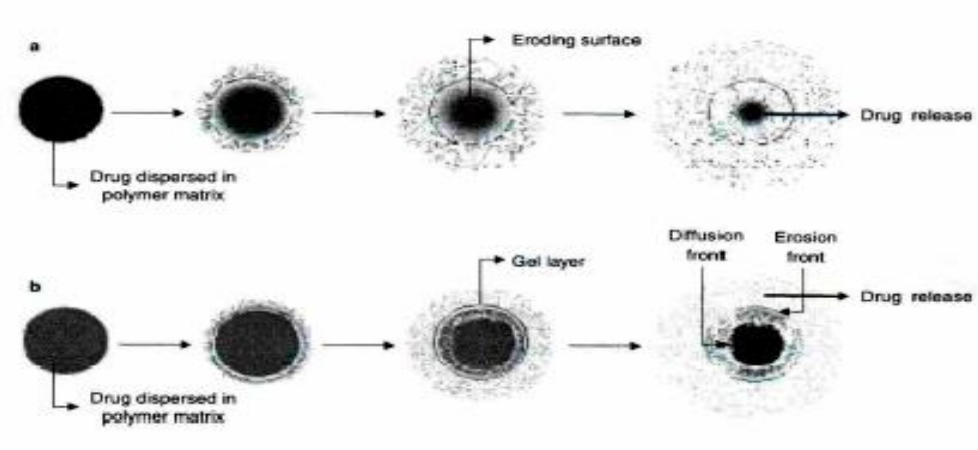


Fig: 1 (a) Drug release controlled by polymer erosion; (b) Drug release controlled by swelling and erosion[14].

A hydrophilic matrix, controlled-release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer **(Fig: 2**). Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion[14].

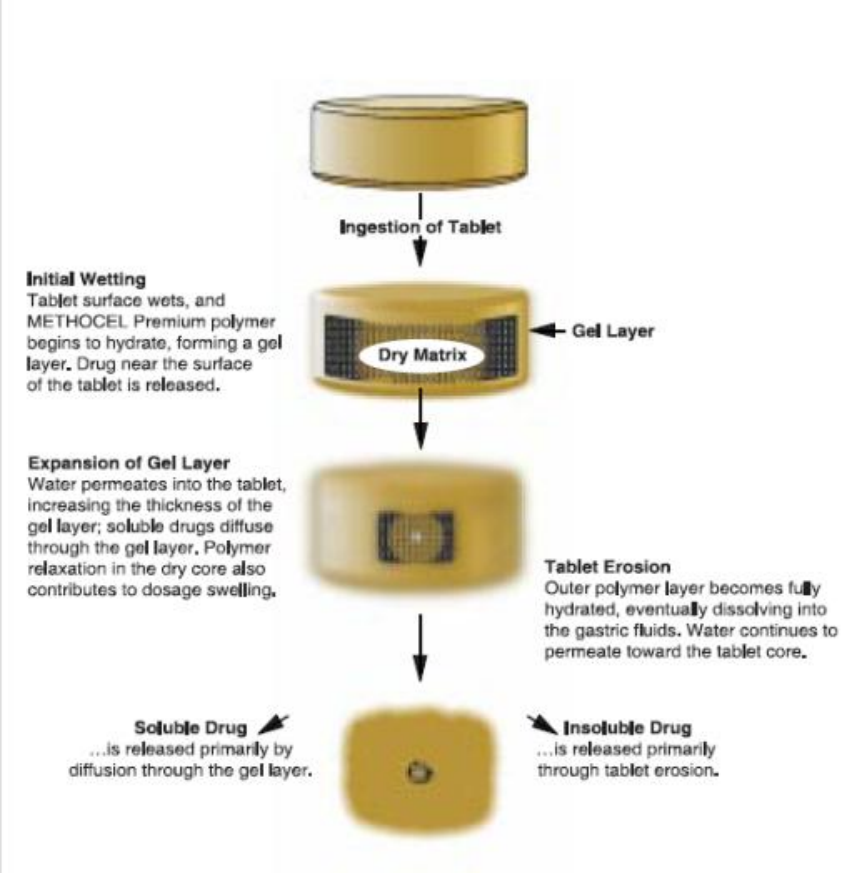


Fig: 2 Mechanism of drug release from matrix gel forming tablets

A detailed description of the swelling, erosion and drug release process can be described as follows:

(i) At the beginning of the process, steep water concentration gradients are formed at the polymer water interface resulting in water imbibation into the matrix. In dry systems the diffusion coefficient is very low, whereas in highly swollen gels it is of the same order of magnitude as pure water. Water acts as a plasticizer and reduces the glass transition temperature (Tg) of the system. Once the Tg equals the temperature of the system, polymer chains undergo the transition from the glassy to the rubbery state as shown in (**Fig: 3)**[15]. The glass transition temperature Tg, of a polymer is an important characteristic constant, in particular with respect to applications in the field of controlled drug delivery. Below the Tg the mobility of the macromolecules is very low. The material is in its glassy state resulting in extremely small diffusion.

(ii) In contrast, above the glass transition temperature the mobility of the polymer chains is markedly increased (rubbery state), leading to much higher mass transfer rates of water and drug. For instance Tg for HPMC is reported to be 154 to 184^{o}C[15].

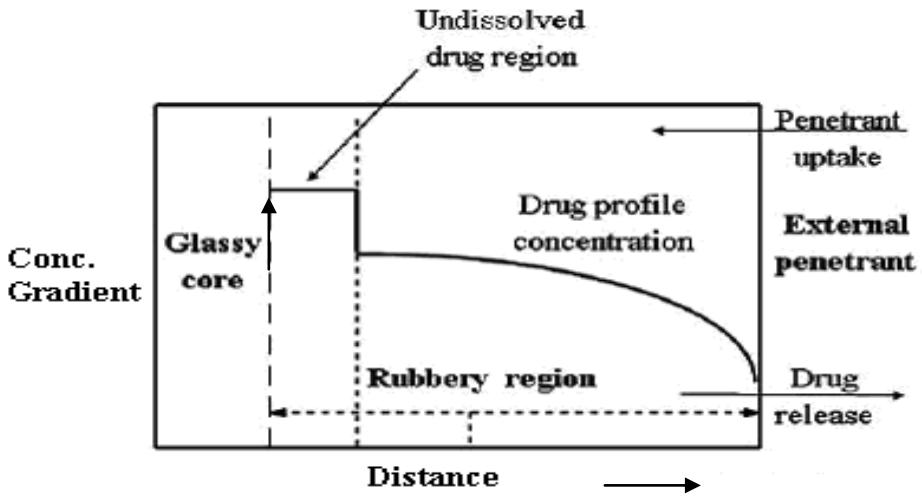


Fig: 3 Drug concentration profile as a function of glass and rubbery regions[16]

(iii) The imbibitions of water and formation of rubbery region; which externally appears as polymer swelling results in dramatic changes of polymer and drug concentrations, and increasing dimensions of the system. The polymer chains unfold, and gradually become solvated, voids created as the polymer unfolds is occupied by water molecules. The apparent volume occupied by these expanded coils is referred to as the hydrodynamic volume.

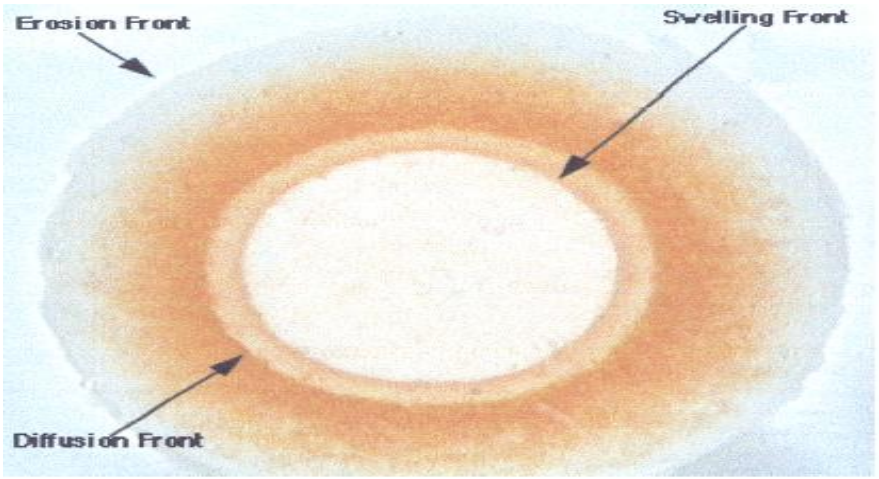


Fig: 4 Different front positions observed during matrix swelling and erosion[17]

(iv) Upon contact with water the drug dissolves and (due to concentration gradient) diffuses out of the device. Three fronts are observed as shown in (**Fig: 4)** The Swelling front, identifying the boundary between the still glass polymer and its rubbery gel state. The boundary between the still undissolved (solid) drug and the dissolved drug in the gel layer is indicated by diffusion front and erosion front identifies the boundary between matrix and dissolution medium. Gao *et al*. (1996) studied the swelling behavior of HPMC matrices using Adinazolam mesylate as the model drug, and concluded that swelling is anisotropic with preferential expansion in the axial direction; swelling is isotropic with respect to the gel layer thickness and composition in both axial and radial directions[17].

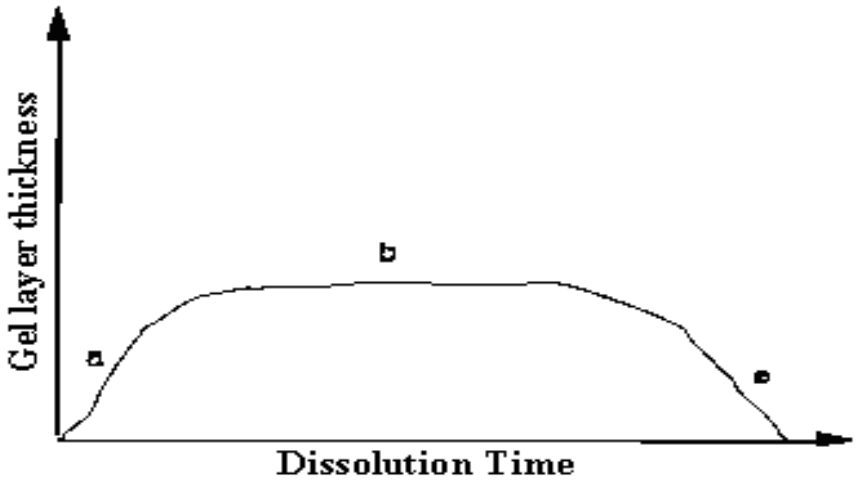


Fig 5: Gel layer thickness as a function of time

(v) With increasing water content the diffusion coefficient of the drug increases substantially. It is to be noted that during drug delivery, as swelling and dissolution of the polymer compete, the gel layer thickness first increases due to swelling (Region **a** in **Fig: 5**), then remains constant due to synchronization of swelling, drug diffusion, and dissolution (Region **b**) and finally decreases (Region **c**) as dissolution takes over.

Thus finally the release of drug is complete as the matrix erodes. The drug release from a swelling matrix system thus can be summed up to be governed by drug diffusion through the matrix and polymer erosion. It is to be noted that in the case of poor water-solubility, dissolved and undissolved drug coexist within the polymer matrix. Undissolved drug is not available for diffusion. In the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion upon drug depletion. Depending on the chain length and degree of substitution of the HPMC type used, the polymer itself dissolves more or less rapidly (erosion of the polymer).

1.7.1.2 Polymer erosion[18]

Polymer chain dissolution from the matrix involves two distinguishable processes as depicted in (**Fig: 6)**.

- The first step involves disentanglement of the individual molecules at matrix surface, which depend on rate of hydration. This occurs at a critical polymer concentration, defined as 'polymer disentanglement concentration. This polymer concentration depends on properties of the polymer and solvent.

- The second step involves the transport of these molecules from the surface across an aqueous diffusion layer, adjacent to the matrix, to the bulk solution[19].

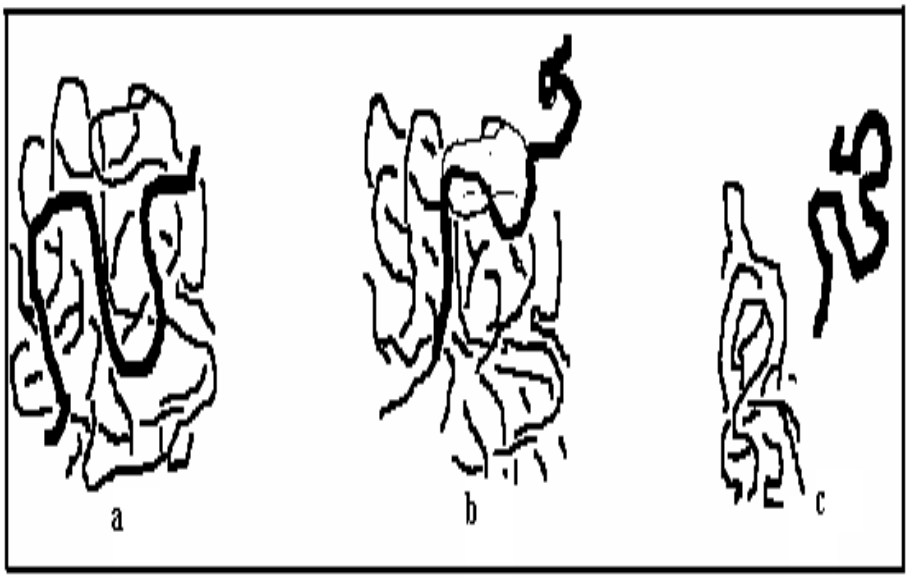


Fig 6: A system showing polymer erosion, (a) initial polymer entanglement in the matrix, (b) repeating chain disentangling from the system and (c) finally disentangling from the system.

1.7.2 Regulatory considerations in extended release products: [19]

- The bioavailability data requirement as specified by FDA for the controlled release products are: The drug product meets the controlled release claims made for it.

- The bioavailability profile established for the drug product rules out the possibility of any dose dumping.

- The drug product's steady-state performance is equivalent to a currently marketed non-controlled release or controlled release drug product with the same active ingredient or therapeutic moiety, which has been subjected to an approved full new drug application.

- The drug product's formulation provides consistent pharmaco-kinetic performance between administrations.

- The reference standard for comparative studies should include one of the following.

1.8 Pharmaceutical coating processes:[20-23]

Basically there are five major techniques for applying coatings to pharmaceutical solid dosage forms:

1. Sugar coating
2. Film coating
3. Enteric coating
4. Fluid bed or suspension coating
5. Compression coating

The present formulation involves enteric coating to protect the drug in the stomach from degradation, which makes the formulation delayed release. Hence the detailed explanation is given on enteric- coating.

1.8.1 *Enteric Coating:* [21]

Enteric coating is a barrier applied to oral medication that controls the location in the GIT region, where it is absorbed. Enteric refers to the small intestine, therefore enteric coatings will dissolve in intestine and prevent release of medication before it reaches small intestine and give desired pharmacological action. The prime intension is to delay the release of drugs which were inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa.

Significance of Enteric coating:

- To protect acid-labile drugs from the gastric fluid.
- To protect from gastric distress or nausea due to irritation of the drug.
- To deliver drugs intended for local action in the intestine.
- To deliver drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed release component to repeat actions.
- Protect the drugs from harmful effect of the gastric contents because some of the drugs are prone to be hydrolyzed in acid media (Eg. Rabeprazole sodium, Esomeprazole, Omeprazole, Oxybutynin chloride).

1.8.2 Enteric Coating Polymers: [22]

Enteric coatings are usually formulated with synthetic polymers that contain ionisable functional groups that render the polymer water soluble at a pH value. Since many of these enteric polymers are esters, they may be subject to degradation (as a result of hydrolysis) when exposed to conditions of elevated temperature and humidity; such hydrolysis can result in a substantial change in enteric properties.

Properties of an Ideal enteric coating polymer:

1. Resistance to gastric fluids.
2. Ready susceptibility to or permeability to intestinal fluids.
3. Compatibility with most coating solution components and the drug substrates.
4. The film should not change on aging.
5. Formation of continuous film.
6. Non-toxicity.
7. Low cost.
8. Ease of application

A polymer with threshold pH in the range of 5 to 6 is considered ideal for an enteric coat. This is based on the premises that the pH of the stomach, even in the fed state, will rarely reach this level but will exceed duodenum, where secretion of bicarbonate neutralize the acidic chyme, leaving the stomach. There is no single polymer that applicable for the enteric coating all drug molecules. The nature of core materials (acidity, basicity or permeability through different enteric polymer films) may limit the choice of polymer.

Cracking of the film either during application or on storage will result in a loss of enteric properties. Therefore, consideration must be given to the mechanical properties of the applied film. Cracking problems can be effectively overcome by plasticization. Plasticizer can also be used to reduce the permeability of the polymer films to water vapor.

The choice of suitable plasticizer is restricted to non-water soluble materials because these are likely to be most effective.

General rule to follow is to use 1 part plasticizer to 10 parts polymer. One should also considered viscosity of the plasticizer, its influence on the final coating solution, its effect on film permeability, tackiness, flexibility, solubility, taste, toxicity, compatibility with other coating solution components, stability of the film and the final coated product.

Most enteric coatings won't dissolve in solutions with a pH lower than 5.5.

Commonly-used enteric coating polymers:

1. Methacrylic acid copolymers.
2. Cellulose acetate (and its succinate and phthalate version).
3. Hydroxy propyl methyl cellulose phthalate.
4. Polyvinyl acetate phthalate.
5. Hydroxy ethyl ethyl cellulose phthalate.
6. Cellulose acetate tetrahydrophtalate.
7. Acrylic resin.
8. Shellac.

1.8.3 Film Coating of Solid Dosage forms: [23]

Film coating is a process that involves the deposition of thin but uniform, polymer film onto the surface of the core tablet. Unlike sugar coating, the flexibility afforded in film coating allows additional substrates, other than just compressed tablets, to be considered for coating (e.g. powder, granules, nonpareils, capsules). Coatings are applied continuously to moving bed of material usually by means of a spraying technique, although manual application procedures have been used. Historically, film coating was introduced in the early 1950 to combat the shortcomings of the then predominant sugarcoating process. Film coating has proved successful as a result of the many advantages offered which includes,

- Minimal weight increase (typical 2 to 3% of tablet core weight)
- Significant reduction in processing times
- Increased process efficiency and output
- Increased flexibility in formulation
- Improved resistance to chipping of the coating
- Cost effectiveness
- Acceptable for diabetic patients

1.8.4 Other additives: [23]

1.8.5 Plasticizer

Plasticizers can modify the physical and chemical properties of the polymers. Optimization of plasticizer must be concentration based on presence of other additives. Some of the commonly used plasticizers are castor oil, propyleneglycol, polysorbates and organic acid esters.

1.8.6. Colorants

Colorants are used to provide distinctive color and elegance to a dosage form. The most common colorants in use are certified food drug and cosmetics colorants. These are synthetic dyes or lakes of dyes.

1.8.7 Solvents

The primary function of a solvent system is to dissolve or disperse the polymers and other additives and convey them to the substrate surface. The most widely used solvents for enteric coating polymers are water, ethanol, isopropanol, chloroform, acetone etc.

1.9 Disease etiology

Urinary incontinence: [24, 25]

An overactive bladder is a condition that results from involuntary contraction of the muscle in the wall of the urinary bladder. Overactive bladder causes a sudden and unstoppable need to urinate (urinary urgency). Overactive bladder is also referred to as urge incontinence and is a form of urinary incontinence (unintentional loss of urine).

Over reactive bladder increases with age approximately more than 65 years and is reported that 5% to 10% of the adult populations and its prevalence increases with age affected by this disorder worldwide, which has impaired quality of life of patients. Antispasmodics are the drugs of choice in treatment of urinary incontinence. Overactive bladder affects an estimated 1 in 11 adults in the United States. Overactive bladder, however, should not be considered a normal part of aging.

The symptoms of overactive bladder include frequent urination, urgency of urination, and urge incontinence. Overactive bladder may cause significant social, psychological, occupational, domestic, physical, and sexual problems. This

Involuntary loss of urine is reportedly experienced by upwards of 95% of women in their reproductive and post-menopausal years.

1.9.1 *Types of urinary incontinence*

- **Stress Incontinence**

Urine leakage occurs with increases in abdominal pressure (hence, mechanical "stress").

- **Urge Incontinence**

Often referred to as "overactive bladder." Inability to hold urine long enough to reach restroom.

- **Mixed Incontinence**

When two or more causes contribute to urinary incontinence. Often refers to the presence of both stress and urge incontinence.

- **Overflow Incontinence**

Leakage or "spill-over" of urine when the quantity of urine exceeds the bladder's capacity to hold it.

- **Functional Incontinence**

Leakage (usually resulting from one or more causes) due to factors impairing reaching the restroom in time because of physical conditions (e.g., arthritis)

1.9.2 Medications that Can Cause Urinary incontinence: [25]

Table: 2 Medications that Can Cause Urinary incontinence.

Medication	Effect On Lower Urinary Tract
Diuretics	Diuresis induced by diuretics may precipitate incontinence. This is particularly relevant in older persons and/or in those with already impaired continence.
Calciumchannel blockers (heart & blood pressure medications)	Calcium channel blockers can reduce smooth muscle contractility in the bladder and occasionally can cause urinary retention and overflow incontinence

1.9.3 Medications

Drugs commonly used to treat incontinence include:

- **Anticholinergics:** These prescription medications calm an overactive bladder, so they may be helpful for urge incontinence. Several drugs fall under this category, including oxybutynin (Ditropan), tolterodine (Detrol), darifenacin (Enablex), fesoterodine (Toviaz), solifenacin (Vesicare) and trospium (Sanctura). Possible side effects of these medications include dry mouth, constipation, blurred vision and flushing.

- **Topical estrogen:** Applying low-dose, topical estrogen in the form of a vaginal cream, ring or patch may help tone and rejuvenate tissues in the urethra and vaginal areas. This may reduce some of the symptoms of incontinence.

- **Imipramine:** Imipramine (Tofranil) is a tricyclic antidepressant that may be used to treat mixed — urge and stress — incontinence.

- **Duloxetine:** The antidepressant medication duloxetine (Cymbalta) is sometimes used to treat stress incontinence.

Chapter 2

Review of Literature

- **Pritam *et al*., (2007)**[26] designed a porous osmotic pump for the release of oxybutynin, containing pore-forming water-soluble additives in the coating membrane which, when comes in contact with water dissolves and forms microporous structure. The effect of different formulation variables such as ratio of drug to osmogent, membrane weight gain, and level of pore former on the in-vitro release was studied. It was observed that the rate of drug release was increased with increase in the amount of osmogent because of the increased water up take which is the driving force for the drug release. The release of oxybutynin was inversely proportional to the membrane weight gain. The mechanism of drug release was found to be zero-order kinetics.

- **Raslamol K *et al*., (2010)**[27] studied the release of oxybutynin chloride from matrix tablets, using different concentrations of polymers (HPMC, EC, PVP, METHOCEL K100) formulated by wet granulation technique. The prepared formulations were evaluated for the release of drug, along with usual physical parameters, and were observed that the formulation containing Methocel K100M shown the release similar to that of marketed tablet. The release of drug was maximum in zero-order, and the mechanism of drug release was observed to be following Korsmeyer-Peppas model.

- **P santi *et al*., (2006)**[28] prepared transdermal films by dissolving in water an adhesive (plastoid), a film former (polyvinyl alcohol), a plasticizer (sorbitol), and the oxybutynin Hydrochloride. Permeation experiments were conducted in Franz-type diffusion cells using rabbit ear skin as barrier .the release profiles showed much higher release in occlusive conditions than in non-occlusive condition.

- **Gayatri Sathyan *et al*.,(2001)**[29] compared the dry mouth a common side-effect observed with immediate-release oxybutynin,and a controlled-release formulation of oxybutyninchloride, is a once-daily oral dosage form that incorporates the OROS technology.The steady state

stereospeci®c pharmacokinetics were alsoestablished for the two formulations and the kinetic-dynamic relationship ofoxybutynin was examined.by a randomized, repeated-dose, double-blind, two-treatment, two period crossover study,with frequent sampling on day 4 to analyse for plasma R- and S-desethyloxybutynin concentrations.the study concluded that Oxy-XL maintains relatively constant plasma drug and metaboliteconcentrations and minimizes frst-pass metabolism of oxybutynin. The metaboliteappears to contribute to dry mouth associated with oxybutynin, and following Oxy-XL metabolite exposure is reduced compared with IR-Oxy. Consequently less dry mouth was observed with Oxy-XL as compared with IR-Oxybutynin .

- **Marvin M Goldenberg *et al*., (1999)**[30] designed an extended-release oral table formulation, OROS oxybutynin which uses osmotic pressure to deliver the drug at controlled rate. The formulation contains a two-part core consisting of a drug layer and "push" layer containing osmotically active components surrounded by a semipermiable membrane with a laser drilled opening. As the water in the gastro intestinal tract enters the tablet the push layer expands and pushes the drug out into the gastro intestinal tract through the orifice. The pharmacokinetic studies have indicated a slow rise in mean plasma concentration 4 to 6 hours after a single dose of OROS followed by maintenance dose of steady concentrations for 24 hours. The efficacy was compared with immediate release formulation showed no adverse effects.

- **Shivanand Pandey *et al*.,(**2009)[31] developed a porous osmotic pump of Oxybutynin containing pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolved, resulting in the formation of a microporous structure. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the *in vitro* release was studied. The release was

inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver oxybutynin at a zero-order rate.

- **Roger R. Dmochowski *et al*.,(2006)**[32] had developed the transcutenaous delivery of Oxybutynin maintaining the efficacy of oral oxybutynin while significantly minimizing side effects (e.g., dry mouth). By avoiding hepatic and gastrointestinal metabolism of oxybutynin, less N-desethyloxybutynin (N-DEO) is produced and this compound is deemed to be responsible for anticholinergic side effects such as dry mouth. This novel oxybutynin formulation offers patients with OAB and urge urinary incontinence a well-tolerated option for managing the symptoms of overactive bladder.

- **Subhash Chandra Bose P *et al*.,(2011)**[33] formulated transdermal patches of Oxybutynin HCl using HPMCK4M, Chitosan, HPMCP, PVP and PVA. FTIR and DSC studies revealed that there was no interaction b etween Oxybutynin HCl and polymers. Gas phase chromatography was carried to estimate the residual Methanol, acetic acid and dichloromethane. The patches were evaluated for their thickness, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, and surface pH. The tensile strength was found higher for formulations containing HPMCP and HPMCK4M. *In vitro* release studies was carried out in 6.6 pH phosphate shown, Patches containing chitosan and HPMCK4M exhibited greater release than the HPMCP, PVP, PVA and HPMCK4M.T he drug release was in the range of 63.8 to 99.9% at 8 hrs. Many of the buccoadhesive systems followed zero-order release kinetics, concluding that buccoadhesive patches of Oxybutynin HCl can be developed as potential controlled release formulations for the treatment of hypertension.

- **David R Staskin *et al*.,(2009)**[34] designed a OTG(oxybutynin topical gel) to provide consistent plasma levels with daily application, favorably altering the circulating N-desethyloxybutynin metabolite:oxybutynin ratio, and to utilize a biocompatible delivery system, thus minimizing both the anticholinergic adverse effects of oral formulations and the application-site skin reactions associated with other forms of transdermal delivery. Oxybutynin topical gel shows efficacious, safe, and convenient alternative to other oxybutynin formulations and other oral anticholinergic medications for the treatment of Over reactive urinary bladder.

- **Bajaj *et al*., (2008)**[36] prepared a novel metered dose Transdermal Spray formulation for Oxybutynin, and the release from a series of ethanol/acetone/methylal based formulations were assessed *in vitro* and the developed formulation was used for delivery from a metered dose spray. Various parameters like spray pattern, particle size distribution, pH, evaporation time, pump seal efficiency test, average weight per metered dose, content per spray and content uniformity were evaluated. Different film forming agents were assessed and carbopol (0.5%) and lutrol (0.1%) were found to give good clarity of solution, evaporation rate, spray pattern and tackiness of the film. Diffusion studies of the optimized formulations through the semipermeable membrane showed the release of drug to the extent of almost 50% over a period of 24 h. It was concluded that the results obtained shown that the metered dose transdermal spray formulation is a promising and innovative therapeutic system for the administration of oxybutynin.

- **A.D.Woolfson *et al*.,(2003)**[36] designed a reservoir device of an itravaginal ring containing oxybutynin silicone elastomer core encased in a non-medicated silicone sheath, manufactured by reaction injection moulding at 50˚C. An unusually high initial burst

release of oxybutynin was observed *in vitro* with a full length core (100 mg drug loading), with subsequent non-zero order drug release. Use of fractional segment cores substantially reduced the burst effect, yielding linear cumulative drug release versus time plots from days 2 to 14. Thus, a 1/8 fractional segmentcore gave a 24 h burst of 11.28 mg oxybutynin and, thereafter, zero order release at the target dose of 5 mg/day over 14days. Two oxybutynin cores, each 1/16 of full length, gave a greater release than a single 1/8 core, due to core segment endeffects resulting in an increased surface area for release. The burst release was investigated by determining drug solubilities in the propan-1-ol product of elastomer condensation cure (390 mg/ml) and in the elastomer itself (13.9–20.21 mg/ ml, bydirect extraction and indirect thermal methods). The high oxybutynin solubilities were considered the major contributors to the burst effect. It was concluded that use of a fractional segment core would allow development of a suitable oxybutynin reservoir IVR.

- **Ranjini V Nellore *et al*.,(1998)**[37] developed extended release matrix Table NOt of metaprolol tartrate using different grades and levels of hydroxypropyl Methylcellulose(Methocel K4M, K15M, k100M, and K100V). Different granulation techniques were evaluated such as direct compression; fluid-bed and high shear granulation. Direct compression formulations exhibited poor flow, picking, and, sticking problems .High-shear granulations resulted in the formation of hard granules but yielded good tablets,Fluid-bed granulations were satisfactory in terms of tablets performance. The release from formulations containing Methocel K100V was found sensitive for changes in polymer concentrations. Thus the results lead to the optimization of MetocelK100V as a rate controlling matrix.

- **N.K jain *et al*.,(2002)**[38] Controlled release (CR) tablets of Diclofenac were developed employing hydroxypropyl methylcellulose 1000 (HPMC-1000) and hydroxypropyl methylcellulose 15000 (K-15 Methocel) as matrices. A priming dose of diclofenac was contained in the first layer and the maintenance dose was in the second layer in the HPMC-1000 or K-15 Methocel matrix to obtain release rates of the drug of approximately 8 mg h^{-1} for an extended period of time. The comparative in vivo evaluation of the K-15 Methocel tablet and Voltarol® 50 (diclofenac 50 mg enteric tablet) in human volunteers showed that, the matrix tablet, a quicker onset of action and a more uniform plasma level of diclofenac around the maximum concentration could be maintained as compared to Voltarol® 50.

- **Eddy Castellanos Gil *et al*., (2006)**[39] developed controlled delivery system for propranolol hydrochloride (PPL). The influence of matrix forming agents (native dextran, hydroxypropyl methylcellulose (HPMC), cetyl alcohol) and binary mixtures of them on PPL release *in vitro* was investigated. The sustained-release matrix tablets with good physical, mechanical and technological properties were obtained with a matrix excipient:PPL ratio of 60:40 (w/w), with a dextran:HPMC ratio of 4:1 (w/w) and with a cetyl alcohol amount of 15% (w/w). The *in vitro* dissolution profiles of sustained-release matrix tablets of racemic PPL were determined and compared with the United States Pharmacopeia (USP) tolerance specifications for Propranolol Hydrochloride Extended-Release Capsules A comparative kinetic study of the present matrix tablets was established. The value for the similarity factor ($f_2 = 69.6$) concluding that the dissolution profile of the present two sustained-release oral dosage forms are similar, and the codependent mechanism of drug release was established.

- **Angel Concheiro *et al*.,(1999)**[40] assessed the potential value of (HPMC) mixtures as gelling agents in matrix tablets for hydrosoluble drugs. Experiments were carried out with Methocel^{R} K100LV (an HPMC with nominal viscosity of 100 cP) and Methocel^{R} K100M (an HPMC with nominal viscosity of 100000 cP). Rheological characterization of 2% dispersions of the polymers, and of 30:70, 50:50 and 70:30 mixtures, indicated that it is possible to obtain a wide range of rheological behaviours by mixing K100LV and K100M, were obtained and that the two polymers display rheological antagonism. Trials were carried out with atenolol tablets made with 40% or 80% gelling agent (i.e. K100LV, K100M or one of the K100LV:K100M mixtures). Analysis of drug dissolution profiles in 0.1 N HCI, on the basis of Higuchi's model and the equation of Korsmeyer and coworkers, indicated that drug release in all cases was diffusion-limited.

- **Rajesh Kaza**, ***et al*.,(2010)**[41] optmized the formulation for the delayed and extended release tablets of mesalamine, by wet granulation technique using the polymers, such as HPMCK-100M, HPMC K4M, HPMCE15 and HPMC E5. It was found that the best formulation showed 98.75 % of drug release at the end of 10 th hour. In-vitro drug release studies of mesalamine delayed and extended release tablets showed that, the rate of the drug release follows first order kinetics as indicated straight line with good correlation coefficient for the plot of log percentage drug remaining vs time. The rate of drug release was found to be dissolution control as there was a good correlation coefficient for the plot of Hixon-Crowell cube–root law.

- **Shinichiro Tajiri *et al*.,(2010)**[42] developed an extended release dosage form of Cevimeline. Two types of extended release tablets(simple matrix table and press-coated tablets) and their potential as extended release dosage forms were assessed. Simple

matrix table have a large amount of hydroxypropylcellulose as a rate controlling polymer and the matrix is homogenous throughout the tablet. The press-coated consista of a matrix core, which was completely surrounded by an outer shell containing large amount of hydroxypropylcellulose .The simple matrix tablets could not sustain the release of Cevimeline effectively. In contrast, the press-coated tablets shoed a slouer dissolution rate compared with the simple matrix tablets and the release curve was nearly linear. The dissolution of Cevimeline from the press-coated tabltes was not markedly affected by the pH of the dissolution medium.

- **Syed Namath Ulla, *et al*.,(2009)** [43] developed Lornoxicam SR matrix tablets that provide complete drug release that starts in the stomach to rapidly alleviate the painful symptoms and continues in the intestine to maintain analgesic effect. Drug-polymer compatibility studies by FTIR gave confirmation about heir purity and showed no interaction between drug and selected polymers. Various formulations were developed by using release rate controlling and gel forming polymers like HPMC (K4M, K15M, K100M) by direct compression method. It was concluded that the release followed zero order kinetics, as the correlation coefficient (R2 value) was higher for zero order release, so the drug release mechanism is controlled release. The best formulation was found to be stable during stability studies for two months. Thus, best formulation satisfied physic-chemical parameters and *in vitro* drug release profile requirements for a sustained drug delivery system.

- **Amelia Avachat *et al*.,(2007)**[44] developed and characterized an oral controlled release drug delivery system for concomitant administration of Diclofenac sodium(DS) and chondroitin sulfate(CS). A hydrophilic matrix-based tablet using different concentrations of HPMC was formulated. The *in vitro* drug release study revealed that HPMC K 100CR at concentration of 40% of

the weight of the dosage form was able to control the release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS. The *in vitro* release data of CS and DS followed Korsmeyer-Peppas and zero order kinetics respectively.

- **Jaleh Varshosaz *et al*.,(2006)**[45] formulated sustained release tablets of highly water-soluble Tramadol HCL. Matrix tablets of Tramadol were produced by direct compression method. Different concentrations of polymers and the combination of polymers (HPMC, Xanthum gum, Guar gum) were applied. After evaluation of physical parameters, the dissolution test was performed in the phosphate buffer media (pH 7.4) up to 8 hours. Tablets with only Xanthum gum had the highest mean dissolution time; the least dissolution efficiency .The release followed zero order models via swelling, diffusion, and erosion mechanism. Guar gum alone could not efficiently control the release while Xanthum gum and all combinations of natural gums with HPMC could retard Tramadol HCL release.

- **Zeng W.M *et al.,(*2004)**[47] developed an oral sustained release matrix formulation of a highly water-soluble drug (Ranitidine HCL). It was designed and developed to achive a 24 hour release profile. Sodium alginate formulaton matrices containing Xanthum gum or zinc acetate or both were investigated. The results showed that the presence of both Xanthum gum and zinc acetate in sodium alginate matrix played a key role in controlling the drug release for 24 hours. Evaluation of the release data showed the release mechanism for the novel formulation might be attributed to the diffusion of the drug.

- **SC Basak *et al*.,(2004)**[47] Propranalol Hydrochloride matrix tablets were prepared with HPMC polymer to control the release of drug with a view to develop sustained release dosage form. The

resulting matrix tablets were prepared with HPMC K4M fulfilled all the official requirements of tablet dosage forms. The *in vitro* drug release was measured for a total period of 12 hours using 1.2pH buffers for first 1 hour and pH 7.5 buffers for the rest of the period. The drug release was within the limits (USP requirements). The results provide a method of achieving sustained drug action through uniform drug release.

- **Shao Z.J *et al.*, (2001)**[48] studied the release of Diphenhydramine HCL matrix tablets composed of PVP and povidone(Kollidon SR). kollidon SR was found to provide a sustained release effect for the model compound, with certain formulation and processing variables playing an important role in controlling its release kinetics. Stability studies conducted at 40˚C/75% RH revealed a slowdown in dissolution rate for the drug –kollidon SR formulation, as a result of polyvinyl acetate relaxation. The release mechanism of kollidon formulation appears to be diffusion controlled,while that of drug-Kollidon-lactose formulation appears to be controlled predominantly by diffusion along with erosion.

- **James L. Ford *et al.*, (1999)**[49] evaluated the relationship and influence of formulation and technological factors such as Drug: HPMC ratio, particle size of the drug, particle size of HPMC and compression force, on drug release from matrices containing HPMC and Diclofenac sodium as a model drug. The influence of these variables was assessed by multi-way analysis of variance. The results of the study point out the rate and mechanism of Diclofenac sodium release from HPMC K15 M matrices are mainly controlled by the Drug: HPMC ratio. The drug and HPMC particle size also influence the drug release parameters, although to a lesser extent. Finally,the independence of the drug release from the matrix tablets with respect to the compression force is reported.

- **Subal C.basak *et al*.,(2010)**[50] enteric coated Aceclofenac matrix tablets were formulated as sustained release tablets employing HPMC. Tablets using different drug polymer ratios of HPMC were prepared by wet granulation technique. Formulation was optimized on the basis of acceptable tablet properties and *in vitro* drug release. Aceclofenac release from tablets was extended from 16 to 24 h from formulated batches.the release kinetics was found to be followed Higuchi model.the tablets shown diffusion dominated drug release.

- **Praveen S. Hiremath *et al*.,(2008)**[51] developed a controlled release (CR) matrix tablet formulations of Rifampicin and Isoniazid combination, a series of formulations were developed with different hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) in varying polymer ratios and procressing techniques. Further, Eudragit L100-55 was incorporated in the matrix tablets to compensate for the pH-dependent release of rifampicin. Rifampicin was found to follow linear release profile with time from HPMC formulations, and with HPC, there was an initial higher release in simulated gastric fluid (SGF) followed by zero order release profiles in simulated intestinal fluid (SIFsp) for Rifampicin. The release of Isoniazid was found to be predominantly by diffusion mechanism in HPMC formulations, and with HPC formulations release was due to combination of diffusion and erosion. From this it was concluded that the initial release was sufficiently higher for rifampicin from HPC thus ruling out the need to incorporate a separate loading dose.

- **James L. Ford *et al*.,(2002)**[52] formulated a sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices .The ratio of promethazine: HPMC was the major rate controlling factor. A straight-line relationship

existed between the Higuchi-type release rate and the reciprocal of the tablet content of HPMC. The study was continued increasing the particle size range of promethazine from 45–63 to 500–700 μm which produced only a 12% increase in the drug release rate. Increase in the compaction pressure does not modify the release. The study concluded that the lowest viscosity grade of HPMC used (HPMC K100) gave the highest release rates at constant HPMC: drug ratio. The other three grades (HPMC K4M, K15M and K100M) also showed similar release rates despite the variation in their molecular size.

- **Efentakis Manuel *et al*., (1990)**[53] modeled the drug release from hydrophobic matrices by use of thermodynamic activation parameters**.** Sustained release tablets of indomethacin were prepared using Eudragit RS. Two types of formulation were considered, one was a directly compressed powder mixture which produced a matrix system, and the other was prepared by granulation, such that the drug was to some extent sealed within a cast film of the polymer. Dissolution studies (USP paddle) revealed that the drug release from the matrix was directly proportional to the concentration of the polymer that was used. Drug release from the granulated system was much slower than from the directly compressed matrix.

- **Sung-Hyun Park *et al*., (2005)**[54] studied the Preparation of an extended-release matrix tablet using chitosan/Carbopol interpolymer complex. A chitosan and Carbopol interpolymer complex (IPC) was formed using a precipitation method in an acidic solution. The chitosan and Carbopol IPC was characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and turbidity measurements. FT-IR demonstrated that the IPC formed a complex through an electrostatic interaction between the protonated amine (NH_3^+)

group of chitosan and the carboxylate (COO^-) group of Carbopol. DSC indicated the IPC to have different thermal characteristics from chitosan or Carbopol. The turbidity measurement revealed the complexation ratio of IPC between chitosan/Carbopol to be 1/4. A theophylline tablet was prepared using the IPC as a matrix material. The drug release profile from this tablet was similar to that from the HPMC tablet and showed a pH-independent release profile. The mechanisms for drug release from the IPC tablet were diffusional release at pH 6.8 and relaxation release at pH 1.2.

- **J. L. Pedraz *et al*.,(2002)**[55] studied the release of ketoprofen enantiomers from HPMC K100M matrices. They studied the sustained release formulation of ketoprofen elaborated with HPMC K100M on the hypothesis that chiral excipient can stereoselectively affect the release of the racemic drug. They observed the differences in the percentage release between enantiomers show the existence of chiral interaction between ketofrofen and HPMC K100M.

- **Dhake A.S *et al*..(2005)**[56] studied the formulation and release characteristics of sustained r elease ofloxacin tablets using HPMC in various ratios. They concluded that HPMC cellulose is an appropriate polymer that can be utilized as matrix forming agent to prolong the release of drug

- **Yihong Qiu *et al*.,(1997)**[57] formulate sustained release hydrophilic matrix of zileuton and perform *in vitro* and in vivo studies. They studied the prototype formulation with drug loading of 50 to 60 % were prepared and tested for *in vitro* using USP appratus I, II and III in absorption of three formulation with different release rate were evaluated in beagle dog. In vivo drug release data were corelated with *in vitro* release and they observed linear

relationships between *in vitro* and in vivo release with more rapid in vivo release than *in vitro*.

- **B. Parthsarthi G *et al*., (2011)**[58] Formulated Omeprazole delayed release tablets. The omeprazole magnesium compressed tablets were optimized for all physical parameters and the,optimized . Eudragit L30D55was selected as enteric coating polymer, and the tablet having tbest dissolution profile for a delayed period of time which shown 102.43% at end of12th hour. The release profile of omeprazole magnesium from enteric coated tablets has shown a slow release following first order kinetic with non- Fickian mechanism. .

- **Anroop B Nair1 *et al*.,(2010)**[59] formulated and evaluated enteric coated tablets for esomeprazole magnesium trihydrate. Different core tablets were prepared and a formulation was selected for further enteric coating, based on the disintegration time.. Enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and Acryl-EZE® to achieve 5% weight gain, coating was optimized to 8% w/w. *In vitro* analysis of the developed tablets was carried out. This study concluded that enteric coated tablets of esomeprazole can be prepared using any of the enteric coating polymer studied using a minimal weight gain of 8%.

Chapter 3

Aim and Objective

Aim of the present investigation

The present investigation relates to the development of extended release matrix tablets containing Oxybutynin Hydrochloride for the treatment of over reactive urinary bladder. Oxybutynin Hydrochloride is an anticholinergic agent, having short half life of (2-3hours) the development of extended release formulations of Oxybutynin Hydrochloride is therefore therapeutic relevance and can be used to provide a consistent dosage through extending an appropriate level of drug over time.

To achieve this goal various prototype formulation trials are taken and evaluated with respect to the various quality control such as dissolution. The formula will be finalized by comparing the *in vitro* dissolution profile with that of the Ditropan tablets.

Reason for selection of delayed release dosage form:

Due to instability in acidic environment, a trail was made to by-pass the stomach by using enteric coating which thereby improves bioavailability and therapeutic efficacy with no degradation of drug.

Objective of the study

The overall objective was

- To formulate and evaluate Extended release tablets of Oxybutynin Hydrochloride.
- To determine the best fit dissolution profile for dosage form.
- To study the release profile of the dosage form and to compare their drug-release profiles with the Ditropan(innovator).
- To study the stability of the optimized formulation

Chapter 4

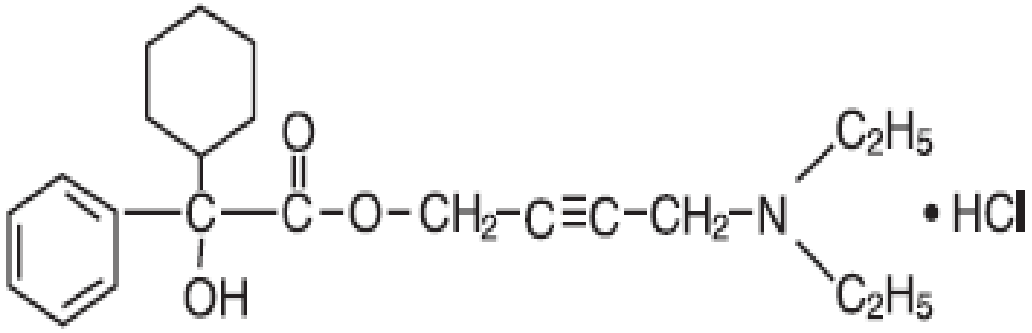
Drug and Excepients Profile

Drug Profile

Oxybutynin Hydrochloride: [60- 64]

Oxybutynin Hydrochloride is an anticholinergic and antispasmodic medication used to relieve urinary and bladder difficulties, including frequent urination and inability to control urination, by decreasing muscle spasms of the bladder. It competitively antagonizes the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor.

Structure:



Chemical name **:** 4-(diethylamino)but-2-yn-1-yl2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride.

Description **:** Oxybutynin chloride ia a white or almost white to crystalline Oxybutynin chloride is a racemate of R- and S- enantiomers.

Molecular formula **:** $C_{22}H_{31}NO_3$.HCL

Melting point **:** 124 °C to 129 °C.

Molecular weight **:** 394.0

Solubility **:** Freely soluble in water and ethanol (96%), Soluble in acetone, slightlysoluble in ether Insoluble in cyclohexane.

BCS Class **:** Class 1

Functional category **:** Antispasmodic In the treatment of over reactive Urinary bladder.

Storage conditions **:** Store in air tight containers, Protect from light.

Pharmaco kinetic parameters: [65, 66]

Absorption:

Following the first dose of oxybutynin chloride extended release tablets, oxybutynin plasma concentrations rise for 4 to 6 hours; and from there steady concentrations are maintained for up to 24 hours.

Distribution:

The apparent volume of distribution is approximately 193 L. The serum protein binding of oxybutynin chloride was about 83-85%, primarily to albumin.

Metabolism:

Oxybutynin Hydrochloride is metabolized primarily by the cytochrome P450 enzyme systems, Particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following oxybutynin chloride extended release tablet administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Elimination:

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Mechanism of action:

Oxybutynin Hydrochloride is an anticholinergic agent, it exerts antispasmodic effect on smooth muscle and inhibits the action of acetylcholine at post ganglionic cholinergic sites, thus increasing bladder capacity and delaying the initial desire to void by reducing the number of motor impulses reaching the detrusor muscle. oxybitynin Hydrochloride does not block acetylcholine effect at skeletal myoneural junctions or at autonomic ganglia; neither does it have effect on the smooth muscle of blood vessels.

Therapeutic Uses:

Urge incontinence, over reactive urinary bladder, nocturnal enuresis.

Dosage:

5mg three times daily to obtain clinical response, in case of nocturnal enuresis a single dose of 5-10mg before bed time can be administered.

Over Dose:

Drowsiness, hallucinations, dilation of pupils,urinary retention.

Storage:

Store between 15^0c to 30^0c.

Contraindications:

- Myasthenia gravis.
- Narrow-angle glaucoma or shallow anterior chamber.

- Gastrointestinal obstruction including paralytic ileus, intestinal atony.
- Patients with bladder outflow obstruction where urinary retention may be precipitated.

Adverse effects

Dry mouth, difficulty in urination, constipation, blurred vision, drowsiness and dizziness. Anticholinergics have also been known to induce delirium.

Use in Specific Populations:

Nursing Mothers:

Oxybutynin chloride and its metabolites are excreted in the breast milk of animals. Oxybutynin chloride excretion in human milk has been detected in a study of a single nursing mother after a single 10 mg oral dose. Approximately 60%, of that found in maternal blood. Therefore breast-feeding mothers should avoid taking oxybutynin.

Pediatric Use:

Oxybutynin chloride is safer in children over five years of age, and may be given in doses up to 5mg twice daily for enruesis without any serious adverse effects. Some facial flushing is experienced by 80%of children when the drug is initially prescribed but this usually subsides after the first month of therapy.

Gender:

There is a modest rise in Oxybutynin chloride AUC and C_{max} in women than men.

Excipients Profile

Hydroxypropyl MethylCellulose[65]

Synonyms: Hydroxypropylmethylcellulose; HPMC; Methocel; Benecel MHPC; methyl hydroxy propyl cellulose; methylcellulose propylene glycol ether; Metolose.

Chemical Name and CAS Registry Number:

Cellulose hydroxy propyl methyl ether [9004-65-3]

Structural formula:

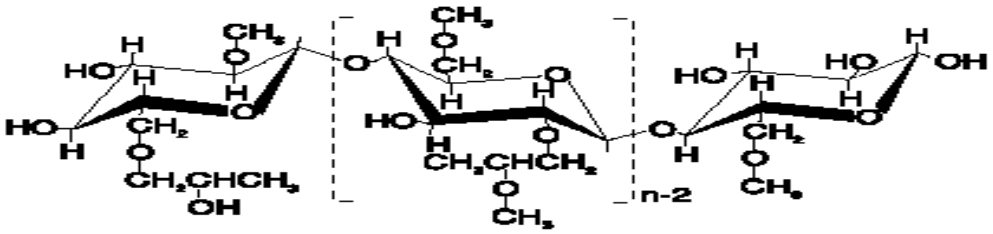


Figure: 7 Structure of HPMC

Functional category:

Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Physicochemical Properties:

Description	**:**	White to off white powder, free flowing powder
Particle size	**:**	Minimum 95% through a #40 US standard sieve
Methoxyl content	**:**	19-24%
Hydroxypropyl content	**:**	7-12%
Bulk density	**:**	0.12 – 0.15 g/ml

pH (1% content) **:** 5.5-8

Solubility **:** HPMC K100M is a high viscosity polymer which is soluble in water.

Table:3 Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow chemical Co.). Viscosity measured at 20^0C

Methocel product	USP 28 designation	Nominal viscosity(mPa s)
Methocel K4 Premium	2208	4000
Methocel K15 Premium	2208	15000
Methocel K100MPremium	2208	100000
Methocel E4M Premium	2910	4000
Methocel F50Premium	2906	50
Methocel E10MPremium	2906	10000
Methocel E5 Premium	2906	5
Methocel E15 Premium	2906	15
Methocel K4 E50Premium	2906	50
Methocel 60SH	2910	50, 4000, 10000
Methocel 90SH	2208	100, 400, 4000, 1500

Stability and storage:

Hypromellose powder is stable material, although it is hygroscopic after drying. Solutions are stable at PH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling. The gel point is 50-90^0C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer

must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well closed container, in a cool, dry place.

Applications:

Hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation process. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Hypromellose is also used as suspending agent in topical formulations. Compared with methyl cellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fiber present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45-1.0% w/w may be added as thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Table:4 Crospovidone[66]

Synonyms	Crospovidonum, Kollidon, Plasdone polyvidone polyvinylpyrrolidone, polyvinylpyrrolidone–vinyl acetate copolymer.
Molecular weight	2500–3 000000
Chemical name	1-Ethenyl-2-pyrrolidinone homopolymer.
Description	Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.
Functional categories	Disintegrant, dissolution aid, suspending agent, Tablet binder in wet granulation.
Solubility	Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydro - carbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution.
Stability,and storage conditions	Powder is hygroscopic; it should be stored in an airtight container in a cool, dry place.
Applications	Carrier for drugs, Dispersing agent, Suspending agent Tablet binder, Tablet diluents or coating agent
Incompatibility	The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes.

Table: 5 Microcrystalline Cellulose[67]

Synonym	Avicel ; cellulose gel; Celphere; Ceolus KG; crystallinecellulose; Emco cel; Ethispheres; Fibrocel; Pharmacel.
Molecular weight	36 000
Description	Microcrystalline cellulose occurs as white, odourless, tasteless, Crystalline powder composed of porous particles,ti is commercially available in different particle sizes and moisture grades.
Functional categories	Adsorbent agent, suspending agent, Tablet and capsule diluents, Tablet disintegrant.
Solubility	Slightly soluble in 5%w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.
Stability and storage conditions	Microcrystalline cellulose is a stable though hygroscopic material. Should be stored in a well-closed container in a cool, dry place.
Applications	**Use** / **Concentration (%)** Tablet binder/diluents 20-90% Tablet sealer
Incompatibility	Incompatible with strong oxidizing agents.

Table: 6 Lactose Monohydrate[68]

Synonyms	Pharmatose, DCL, Lactochem, Tablettose, Granulac, SpheroLac, Capsulac, Sachelac.
Chemical Name	O-b-D-galactopyranosyl-(1!4)-b-D-glucopyranose
Empirical Formula	C12H22O11
Molecular weight	360.31
Description	White to off white crystalline particles or powder.it is odour less and slightly sweet as sucrose.
Functional categories	Binding agent, diluents for dry-powder inhalers, Tablet binder, Tablet and capsule diluents.
Solubility	practically insoluble in chloroform, ethanol , Soluble in water
Stability and storage conditions	Lactose may develop a brown colouration on storage. Lactose should be stored in a well-closed container, protected from light, in a cool, dry place.
Applications	Anhydrous lactose is widely used in direct compression and as a Tablet and capsule filler and binder. Anhydrous lactose is used for moisture-sensitive drugs due to its low moisture content.Monohydrate; Lactose, Spray-Dried.lyophilization aid.
Incompatibility	Lactose is also incompatible with amino acids, aminophylline,Amphetamines, and lisinopril.

Table: 7 Lubritab[69]

Synonyms	Hydrogenated cotton seed oil(Stereotex),hydrogenated palm oil(softisan), Hydrogenated soyabean oil(lipovol).
Molecular weight	38 000
Description	white to yellowish-white with the powder gradesappearing more white coloured than the coarser grade.Hydrogenated vegetable oil type 1 occurs as fine powder, flakes or pellets,
Structural formula	R1COOCH2—CH(OOCR2)—CH2OOCR3
Functional categories	Tablet and capsule lubricant; Tablet binder.
Solubility	soluble in chloroform, petroleum spirit, and hot propan-2-ol; practically insoluble in water.
Stability and storage conditions	Hydrogenated vegetable oil type I is a stable material; typically it is assigned a 2-year shelf-life. The bulk material should be stored in a well-closed container in a cool, dry place.
Applications	It is also used as the matrix forming material in lipophilic-based controlled release formulations.it is used as tablet lubricant in 1-6% concentration.
Incompatibiliy	Incompatible with strong oxidizing agents.

Table: 8 EUDRAGIT L30 D55[70]

Synonyms	Methacrylic acid copolymer, Eastacryl, Eudragit, Ploy Methacrylates, Kollicoat.
Chemical name	Poly(methacrylic acid, ethyl acrylate) 1 : 1
Molecular weight	250,000.
Description	Milky-white liquid of low viscosity with a faint characteristic odor.
Functional categories	Channeling Agent, Enteric coating polymer.
Solubility	The dispersion is miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy, viscous solution is obtained by mixing 1 part EUDRAGIT® L 30 D-55 with 5 parts acetone, and also in isopropyl alcohol.
Stability and storage conditions	Store at controlled room temperatures (USP, General Notices). Protect against moisture. Any storage between 8 ° and 25 °C fulfils this requirement
Applications	It is used as channeling agent. And it is also used as Enteric coating polymer.
Incompatibility	Incompatibilities occur with some polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent electrolytes, pH changes, some organic solvents, and extremes of temperature

Table: 9 Tri Ethyl Citrate[71]

Synonyms	Citric acid, ethyl ester,Citroflex, Citrofol, Hydagen, TEC.
Chemical Name	2-Hydroxy-1,2,3-propanetricarboxylic acid, triethyl ester
Empirical Formula	$C_{12}H_{20}O_7$
Molecular weight	276.29
Description	Triethyl citrate is a clear, odorless, practically colorless, oily liquid
Functional categories	Plasticizer, solvent.
Solubility	Soluble 1 in 125 of peanut oil, 1 in 15 of water. Miscible with ethanol (95%), acetone, and propan-2-ol.
Stability and storage conditions	Triethyl citrate should be stored in a closed container in a cool, dry location.
Applications	Triethyl citrate and the related esters acetyltriethyl citrate, tributyl citrate, and acetyltributyl are used to plasticize polymers in formulated pharmaceutical coatings, Triethyl citrate is also used as a direct food additive for flavoring, for solvency, and as a surface active agent
Incompatibility	Triethyl citrate is incompatible with strong alkalis, and oxidizing agents.

Chapter 5

Plan of Work

Plan of Work

The proposed research work is planned as follows

- ❖ API characterization
- ❖ Preformulation studies
  - ➢ Angle of repose,
  - ➢ Bulk density,
  - ➢ Tap density,
  - ➢ Compressibility index,
  - ➢ Hausner's Ratio,
  - ➢ Compatibility studies,
  - ➢ Sieve Analysis,
- ❖ Formulation and development of Extended release tablet
- ❖ Evaluation of tablets.
  - ◆ Physical parameters like diameter, thickness, hardness, friability,
  - ◆ Determination of drug content
  - ◆ *In-vitro* drug release studies
  - ◆ Determination of release kinetics.
  - ◆ Selection of formulation on the basis of *in-vitro* tools.
  - ◆ Comparison of formulations with Ditropan & selection of best batch.
  - ◆ Stability study by ICH guidelines.

Chapter 6

Materials and Methods

Table: 10 List of Materials used in the study

S.No	Ingredients	Manufacturer	Supplier
1.	**Oxtbutynin Hydrochloride**	Aurobindo Pharma Ltd India	Aurobindo Pharma Ltd
2.	**Methocel K100M**	The Dow chemical company USA	The Dow chemical company USA
3.	**Kollidon 90F**	M/S Isp Technology USA	Anshul Agencies, Mumbai.
4.	**Microcrystalline Cellulose pH102**	Ferro Corporations, USA	Signet Chemical Corporation, Mumbai
5.	**Pharmatoe 200**	Ferro Corporations, USA	SD Fine Chemicals ltd
6.	**Lubritab**	DMV Fonterra Excipients USA	Kamarlal & Co, Hyderabad
7.	**Magnesium Stearate**	M/S Luzenac Varchisone, Italy	Signet Chemical Corporation, Mumbai
8.	**Isopropyl alcohol**	M/S Isp Technology USA	Anshul Agencies, Mumbai.
9.	**Eudragit L30 D55**	Ferro Corporations, USA	Shree Narsimha Chem. Pharma Pvt. Ltd., Maharashtra
10.	**Opadry**	DMV Fonterra Excipients USA	SD Fine Chemicals ltd
11.	**Triethyl citrate**	DMV Fonterra Excipients USA	SD Fine Chemicals ltd

Table: 11 List of Equipments used in the study

S. No.	EQUIPMENT	MANUFACTURER
1	**Granson Vibratory Sifter**	Granson, Mumbai[Aux 220]
2	**Rapid Mixer Granulator**	Scucal, Ahmedabad [RMG 4828L]
3	**Tab density Tester**	Electro lab,Mumbai [ETD 1020]
4	**Homogenizer**	Remi, Thane [R 012]
5	**Double Cone blender**	Vamp,Thane [Double cone]
6	**Laboratory Stirrer**	PMDC Geared [RDT 124A]
7	**Automatic Coating System**	Neomachines, Kolkata [NEOCOTA -5T]
8	**Rapid dryer**	Retsch, Hyderabad [TG-200]
9	**pH Meter**	Thermo ,Mumbai [ORION 2STAR]
10	**Dissolution test apparatus USP Type II**	Lab India [101]
11	**Stability chambers**	Thermo,Mumbai
12	**Hardness tester**	BenchSaven [TM-Series]
13	**Roche Friabilator**	Electro lab,Mumbai [EF-TW]
14	**Tablet Compression machine-16 Station**	Cadmech Machinery co. Pvt.Ltd, Ahmedabad[CMD3-16]
15	**Sieve Shaker**	Retsch, Hyderabad [FR-019]
16	**Weighing Balance**	Essae, Bangalore [DS-852]

6.1 EXPERIMENTAL

Preformulation Study:

Preformulation study can divided into two subclasses

1. API characterization,

2. Compatibility study

6.1.1 Active pharmaceutical ingredient (API) characterization:

These are preliminary characteristics of any substance which is useful in identification of specific material. Following physical properties of API were studied.

Organoleptic Evaluation : Oxybutynin Hydrochlorideis a white to off-white Crystalline powder.

Solubility Analysis : Freely soluble in water and ethanol (96%)

Melting Point : 124 ºc – 129 ºc

Loss on drying:

1.0 g of sample of Oxybutynin chloride was accurately weighed and the powder was kept in a moisture balance apparatus for 5 min, at 105ºCand the moisture content was calculated.

6.1.2 Angle of repose: [72]

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it

slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\tan \theta = h/r$$

Where; θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Angle of repose less than 30^0 shows the free flow

6.1.3 Bulk density:

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

30 g powder blend introduced into a dry 100 mL cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the formula:

$$\rho_b = M / Vo$$

Where, ρ_b = Apparent Bulk Density

M = weight of sample

V = apparent volume of powder

6.1.4 Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2 % and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm per mL, using the formula:

$$\rho_{tap} = M / V_f$$

Where, ρ_{tap} = Tapped Density

M = Weight of sample

V_f = Tapped volume of powder

6.1.5 Compressibility index:

The Compressibility Index (Carr's Index) is a measure of the flow property of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = $[(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$

Where, ρ_b = Bulk Density

ρ_{tap} = Tapped Density

Table: 12 Correlation between Carr's index values and flow properties of Powders

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
>40	Extremely Poor

6.1.6 Hausner's ratio:

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table: 13 Correlation between Hausners ratio values and flow properties.

Hausners ratio	Properties
1.0-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair and aid not needed
1.35-1.45	Poor must agitate
> 1.5	Poor
Above 2	Extremely Poor

6.1.7 Drug Excipient Compatibility Studies:

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Procedure:

Drug is mixed with excipients in different ratio. These mixtures were kept in a 5ml glass vials and packed properly. These vials are exposed to 40˚ C / 75 % RH. Observations for physical appearance are made at initially, 2 week, and 4week, the samples were withdrawn for analysis of following parameter:

1. Appearance and physical conditions
2. IR Analysis.

6.1.8 Sieve Analysis:

The procedure involves the Electromagnetic Sieve shaking of the sample through the series of successively arranged sieves (sieve no. - 25, 30, 40, 60, 80,100 and pan weight), and weighing of the portion of the sample retained on each sieve and calculate percentage retained on each sieve.

6.2 Formulation Study:

Formulation Development of Oxybutynin hydrochloride Extended release Tablets:

Based on preformulation data wet granulation method was selected due to poor flow properties and other characteristics from preformulation and different formulation trials are tabulated below. The excipients selected based on compatibility study and are commonly used excipients.

In the trials different binder, Lubricant, concentrations is taken and compressed the tablets at different conditions and observer the change

6.2.1 Table: 14 Formulation development of Oxybutynin Hydrochloride Extended Release tablets

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Oxybutynin Chloride	15	15	15	15	15	15	15	15	15
MethocelK100M CR grade	80	70	50	55	60	50	45	40	40
Kollidon 90F	--	--	10	5	--	--	--	--	--
Pharmatose 200 M	50	65	70	70	70	80	85	90	90
Avicel PH 102	45	45	45	45	45	45	45	45	45
Isopropyl Alcohol	--	--	q.s	q.s	--	--	--	--	--
Purified water	--	--	--	--	q.s	q.s	q.s	q.s	q.s
Lubritab	10	8	8	8	6	6	6	6	6
Magnesium stearate	--	2	2	2	4	4	4	4	4
Eudragit L30D55	4.5	4.5	4.5	9	9	9	9	9	9
Triethyl citrate	0.5	0.5	0.5	0.5	1	1	1	1	1
Opadry	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25

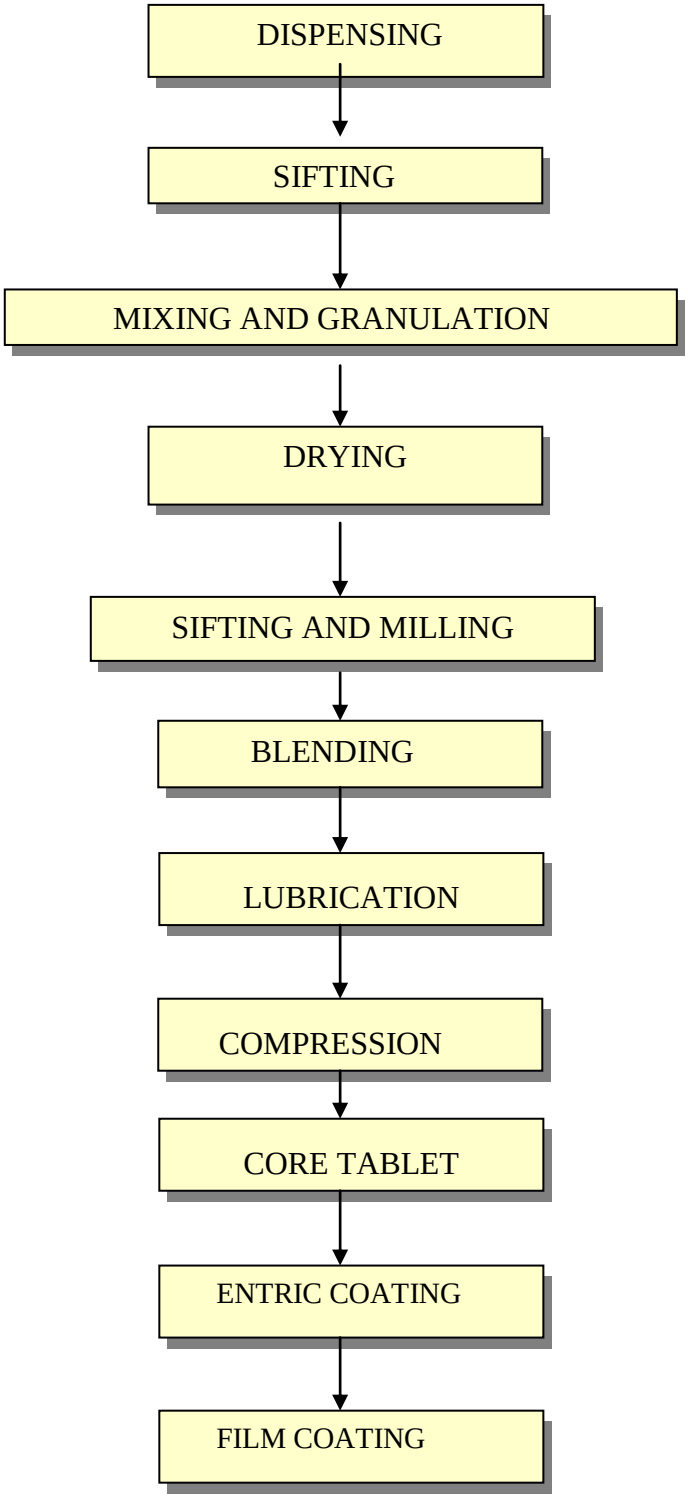


Fig: 8 Flow Chart for Manufacturing Process.

6.3 Procedure:

6.3.1 Sifting:

Oxybutynin Hydrochloride, MethocelK100M, pharmatoze200, and avicel101 and sifted through #40 mesh are collected separately.

6.3.2 Dry mixing:

Mixing was done in RMG (2.0 Lt Capacity) for 10 min with impeller slow speed and chopper off.

6.3.3 Granulation:

6.3.3.1 Binder addition:

The binding solvent 100g in two proportions of 50g was added for 45sec with the impeller slow and followed by the addition of 50g for 45sec with the impeller speed and chopper slow.

6.3.3.2 Granulation:

Binder solution added slowly for 90 sec with chopper off and impeller fast. Then Rinse the vessel and add for 60 sec. Then kneading carried out for 120 sec with chopper slow and impeller fast.

Table: 15 Considerations in Granulation.

Condition	Time	Impeller Speed	Chopper
Dry Mixing	1200 sec	100 rpm	0
Solvent Addition	40 sec	150 rpm	0
Mixing time	60 sec	150 rpm	0
Kneading Time	120 sec	150 rpm	1000 rpm
Removal	60 sec	100 rpm	0

6.3.3.3 Drying:

1. Wet mass was dried in rapid mixer dryer at 60°C until the loss on drying was not more than 2 % w/ w. (Determined by Moisture analyzer at 105°C)

2. Pooled sample from different locations of rapid mixer Dryer bowl were taken and Loss on Drying (LOD) was studied at 105° C on Moisture Balance the LOD after drying was - below 2%.

6.3.3.4 Milling & sifting:

Dried granules were sifted through # 60 and the retentions were milled through 1.0 mm screen, medium speed with knives forward direction in comminuting mill. The milled material was sifted through # 30 mesh. Process continued till all the dried granules pass through # 30 mesh.

6.3.3.5 Blending:

The sifted granules of above step were first mixed with the extra granular quantity lubritab, magnesium stearate (sifted through # 60 mesh) . The blend was mixed in a double cone blender unloaded and compressed into tablets.

6.3.3.6 Compression:

Compression was done using 7.2mm standard concave shaped plain dies.

Tablet compression parameters:

Weight of the Tablet	**:**	200 mg
Hardness range	**:**	12-14 kP
Thickness ranges	**:**	3.82 ± 0.3 mm.

There are various in process control parameters should be performed.

6.3.3.7 During tablet compression:

Appearance

Weight uniformity

Friability

6.4 ***Enteric Coating:***

Procedure for Enteric coating of tablets:

1. Enteric coating solution was prepared by slowly dispersing EudragitL30D55 in water and homogenize for 30 minutes.

2. The dispersion was sifted through muslin cloth and collected into a stainless steel vessel.

3. The enteric coating dispersion was started spraying with following parameters.

6.4.1 Enteric coating Parameters:-

Inlet Temperature	**:**	45-50^{0}C
Exhaust Temperature	**:**	38-42^{0}C
Atomization	**:**	1.2 kg/Cm^2
Pan Rotation	**:**	8-11
Spray rate	**:**	2-5gm/min
Needle gun pressure	**:**	0.8 mm.

The dispersion was kept under continuous stirring, during the coating process. The coating was continued till target weight build up was achieved.

4. After target build up was achieved the pan speed was reduced and spraying of enteric coating dispersion was stopped and the tablets were warmed at the temperature of 38°C – 40°C for one hour.

5. The enteric coated tablets were collected into a container.

6.4.2 Description of Enteric coated tablets:

White, round shaped, concave tablet and plain on both sides.

6.4.3 Evaluation of Core and Enteric coated tablets:

6.4.3.1 Thickness:

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier calipers. Average thickness and standard deviation values were calculated.

6.4.3.2 Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

6.4.3.3 Friability Test:

From each batch, 10 tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% Friability was calculated as follows

% Friability = $(W_1 - W_2) \times 100/W_1$

Where, W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 1 % are generally acceptable.

6.4.3.4 Weight Variation Test:

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = $(W_A - W_I) \times 100/ W_A$

As the total tablet weight was 200 mg, according to IP 2010, out of twenty tablets ± 10 % variation can be allowed for not more than two tablets.

According to USP 2004, ± 10 % weight variation can be allowed for not more than two tablets out of twenty tablets**.**

6.5 Film Coating:

6.5.1 Procedure for Film coating of Enteric coated tablets:

1. Film coating solution was prepared by slowly dissolving opadry in water and homogenize for 45minutes.

2. The solution was sifted through muslin cloth and collected into a stainless steel vessel.

3. The Film coating solution was started spraying with following parameters.

6.5.2 Film coating Parameters:-

Inlet Temperature	**:**	60˚C
Exhaust Temperature	**:**	42^0C-45˚C
Atomization	**:**	1.5kg/Cm^2
Pan Rotation	**:**	8-10
Spray rate	**:**	2-5gm/min
Needle gun pressure	**:**	0.8 mm.

The solution was kept under continuous stirring, during the coating process. The coating was continued till target weight build up was achieved.

4. After target build up was achieved the pan speed was reduced and spraying of Film coating solution was stopped and the tablets were warmed at the temperature of 38°C – 40°C for one hour.

5. The enteric coated tablets were collected into a container.

6.5.3 Description of film coated Tablets:

White, round shaped, concave tablet and plain on both sides.

6.6 Preparation of Standard Curve:

6.6.1 Standard plot using 6.8 pH phosphate buffer:

Accurately weighed quantity (100mg) of Oxybutynin Hydrochloride was taken and dissolved in 10 ml of water in standard flask and made up to 100 ml with phosphate buffer pH 6.8 (1000 ug/ml concentration). From this 1 ml was taken and made up to 100 ml with phosphate buffer pH 6.8, it was used as stock solution . From the above stock solution 1ml, 2 ml, 3 ml, 4 ml and 5ml were taken and diluted to 10 ml, with phosphate buffer pH 6.8 to produce concentration of 1µg/ml, 2 µg/ml, 3µg/ml, 4 µg/ml, 5 µg/ml. The absorbance of the resulting solutions was measured at 220 nm using UV-spectrophotometer with phosphate buffer pH6.8 as blank.

Standard curve was plotted by taking concentration on X-axis and absorbance on Y-axis.

6.6.2 Standard plot using 0.1 M HCl:

Accurately weighed quantity (100mg) of Oxybutynin Hydrochloride was taken and dissolved in 10 ml of water in standard flask and made up to 100 ml with 0.1M HCl (1000 µg/ml concentration). From this 1 ml was taken and made up to 100 ml with 0.1M HCl , it was used as stock solution . From the above stock solution 1 ml, 2 ml, 3 ml, 4 ml, and 5 ml, were taken and diluted with 0.1M HCl to produce concentration of 1µg/ml, 2µg/ml, 3µg/ml, 4µg/ml and 5µg/ml,. The absorbance of the resulting solutions was measured at 220 nm using UV-spectrophotometer with 0.1 M HCl as blank. Standard curve was plotted by taking concentration on x-axis and absorbance on y-axis.

6.6.3 Evaluation of Oxybutynin Hydrochloride enteric coated Tablets:

- Acid resistance
- Assay
- Dissolution (acid stage followed by buffer stage)

6.6.4 Procedure for preparation of solutions:

0.1 M Hydrochloric acid:

Dilute 8.5 ml of Hydrochloric acid with purified water to 1000 ml.

pH 6.8 Phosphate buffer: Transfer accurately 250 ml of 0.2M monobasic potassium phosphate and 112.0 ml of 0.2M Sodium hydroxide to a suitable container and dilute to 1000 ml with purified water.

pH 6.8 Buffer preparation: Dissolve 8.77g of Dipotassium hydrogen orthophosphate (K_2HPO_4) in 500 ml of Milli-Q water. Dilute to 1000 mL with Milli-Q water and adjust the pH of the solution to 6.8 with ortho Phosphoric acid. Filter through 0.45 µm pall Pharma lab Nylon 66 membrane filter.

6.6.5 Acid Resistance Test:

Parameters:

Medium	:	0.1 M HCl
Volume	:	900 ml
Apparatus	:	USP-II, paddle
Speed	:	50 rpm
Temperature	:	37 ± 0.5^0C

Procedure:

Place the tablet in the basket; note the initial and final weights of the tablet. Physical observations were done on the tablet and write the condition of it.

6.7 ASSAY :

6.7.1 Procedure for Assay of Oxybutynin hydrochloride:

6.7.1.1 Preparation of standard solution:

Weigh a quantity of 10mg standard oxybutynin Hydrochloride powder and transfere into 100ml volumetric flask and dilute it to 100ml with methanol.pippet out 1 ml of the above solutiion to 10ml volumetric flask and make up the volume with methanol.

6.7.1.2 Preparation of Sample solution:

Weigh a quantity of the tablet powder equivalent to 10mg of oxybutynin Hydrochlorideand transfer into 100ml volumetric flask and dilute it to 100ml with methanol.pippet out 1 ml of the above solutiion to 10ml volumetric flask and make up the volume with methanol.

The absorbance of the above standard and sample was measured using UV spectroscopy at 220nm.

6.8 Dissolution Studies:

The dissolution was carried out for different experimental trials and also for the Ditropan. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following medias.

6.8.1 Acidic Stage:

Medium : 0.1M HCl

Type of apparatus : USP - II (paddle type)

RPM : 50

Volume : 900 ml

Temperature : 37º C ± 0.5

Time : 2 hrs

6.8.2 Buffer Stage:

Medium : pH 6.8 Phosphate buffer

Type of apparatus : USP - II (paddle type)

RPM : 50

Volume : 900 ml

Temperature : 37ºC ± 0.5

Time : 24hours

6.8.3 *in vitro* drug release studies:

in vitro drug release studies were carried out using USP dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±0.5°C for 24hrs, at 50 rpm, pH 6.8 ±0.2 phosphate buffers as dissolution medium.

Sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and concentration of drug in each sample was analyzed and cumulative percent drug release was calculated. The commercial Ditropan XL tablets were used as the reference formulation.

6.9 Release kinetics[73-75]

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi's model)
3. Cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyers model)

6.9.1 Drug release kinetics-model fitting of the dissolution Data:

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some

analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers-peppas models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor *(f_1)*, similarity factor *(f_2)* can be used to characterize drug dissolution / release profile.

6.9.1.1 Zero-order kinetics:

A zero-order release would be predicted by the following equation.

$$\mathbf{At = A_o - K_o t} \qquad \text{eq (1)}$$

Where,

At = Drug release at time t

A_o = Initial drug concentration

K_o = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to k_o.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

6.9.1.2 First-order kinetics:

A first order release would be predicted by the following equation.

$$\text{Log C} = \text{Log Co} - K_t / 2.303 \qquad \text{eq(2)}$$

Where

C = Amount of drug remained at time t

C_o = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

Use: The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes

6.9.1.3 Higuchi model:

Drug release from the matrix devices by diffusion has been described by following higuchis classical diffusion equation.

$$\mathbf{Q = [DE/ \tau(2A- ECs) C_{st}]} \qquad \text{eq(3)}$$

Where

Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_s = The solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$$\mathbf{Q = K_t ½} \qquad \text{eq (4)}$$

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

Use: The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs.

6.9.1.4 Korsmeyer Peppas model:

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$\mathbf{M_t / M_{\acute{a}} = Kt^n} \qquad \text{eq (5)}$$

Where,

$M_t / M_{\acute{a}}$ = The fraction of drug released at time‘t’

K = Constant incorporating the structural and geometrical Characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\mathbf{Log\ M_t / M_{\acute{a}} = Log\ K + n\ Log\ t} \qquad \text{eq (6)}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for fickian release, > 0.45 and < 0.89 for non-Fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release.

6.9.2 Similarity Factor and Difference Factor Calculation

The similarity factor (f_2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and Ditropan release profiles".

Dissimilarity or difference factor (f_1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and Ditropan release profiles are identical and increases proportionally with the dissimilarity between the two profiles.

There are several methods for dissolution profile comparison. f_2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f_1 & f_2.

$$f_1 = \{ [\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1}^{n} R_t] \} . 100 \qquad \text{eq (1)}$$

$$f_2 = 50. \text{Log} \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\} \qquad \text{eq (2)}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time point of the Ditropan & test product respectively. The factor f_1 is proportional to the average difference between the two profiles, where as factor f_2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f_2 and its significance is shown in the following.

Table: 16 Similarity factor *f2* and its significance

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and Ditropan profiles are dissimilar.
2.	50 -100	Test and Ditropan profiles are similar.
3.	100	Test and Ditropan profiles are identical.
4.	>100	The equation yields a negative value.

6.9.3 Stability Study: [76-78.]

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH guidelines.

Storage Conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life.

Chapter 7

Results

Preformulation :

API characterization:

Initial weight of API taken = 20 gm

Initial volume of API taken = 65 ml

Volume after 500 tap = 47 ml

Volume after 750 tap = 47 ml

Table: 17 Analysis of physical properties of Oxybutynin Hydrochloride

Parameter	Value	Unit
LOD	1.5	% w/w
BD	0.198	gm/ml
TD	0.353	gm/ml
CI	43.75	%
HR	1.78	----
Angle of repose	32.3	^{o}c

Sieve Analysis:

The procedure involves the Electromagnetic Sieve shaking of the sample through the series of successively arranged sieves (sieve no. , 40, 60, 80,100,120 and pan weight), and weighing of the portion of the sample retained on each sieve and calculate percentage retained on each sieve.

Table: 18 Results of sieve analysis of Oxybutynin Hydrochloride

Sieves	Initial weight	Final Weight	Difference weight(gms)	Retained Percentage	Cumulative Percentage
#40	162.5	162.5	0	0	0
#60	167.5	167.5	0	0	0
#80	166.0	167.0	1.0	2	2
#100	152.0	154.0	2.0	4	6
#120	149.5	152.5	2.0	4	10
#Pan	142.0	168.0	26.0	52	100

Drug excipient compatibility studies:

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Procedure:

Drug is mixed with excipients in different ratio. These mixtures were kept in a glass amber colored vials and packed properly. These vials are exposed to 40˚c / 75 % RH. Observations for physical appearance are made at initially, 2 week, and 4week, the samples were withdrawn for analysis of following parameter:

1. Appearance
2. IR Spectra

Table: 19 Differnet ratios of Drug and excipient taken for Compatibility Study

Name of the Excipients	Ratio	Initial	Final observation		Conclusion
			40 ° C / 75 % RH		
			2nd week	4th week	
Oxybutynin chloride		White to off white	White to off white	White to off white	Compatible
Oxybutynin chloride: Methocel k100M	1:1	White to off white	White to off white	White to off white	Compatible
Oxybutynin chloride: Kollidon90F	1:1	white	White	white	Compatible
Oxybutynin chloride: (avicel101)	1:1	white	White	White	Compatible
Oxybutynin chloride: LubritabL30D55	1:1	white	White	White	Compatible
Oxybutyninchloride: Tri ethyl Citrate	1:1	white	White	White	Compatible
Oxybutynin chloride: Isopropyl alcohol	1:1	white	White	white	Compatible
Oxybutynin chloride: Magnesium Stearate	1:1	white	White	White	Compatible
Oxybutynin chloride: opadry white	1:1	white	White	white	Compatible

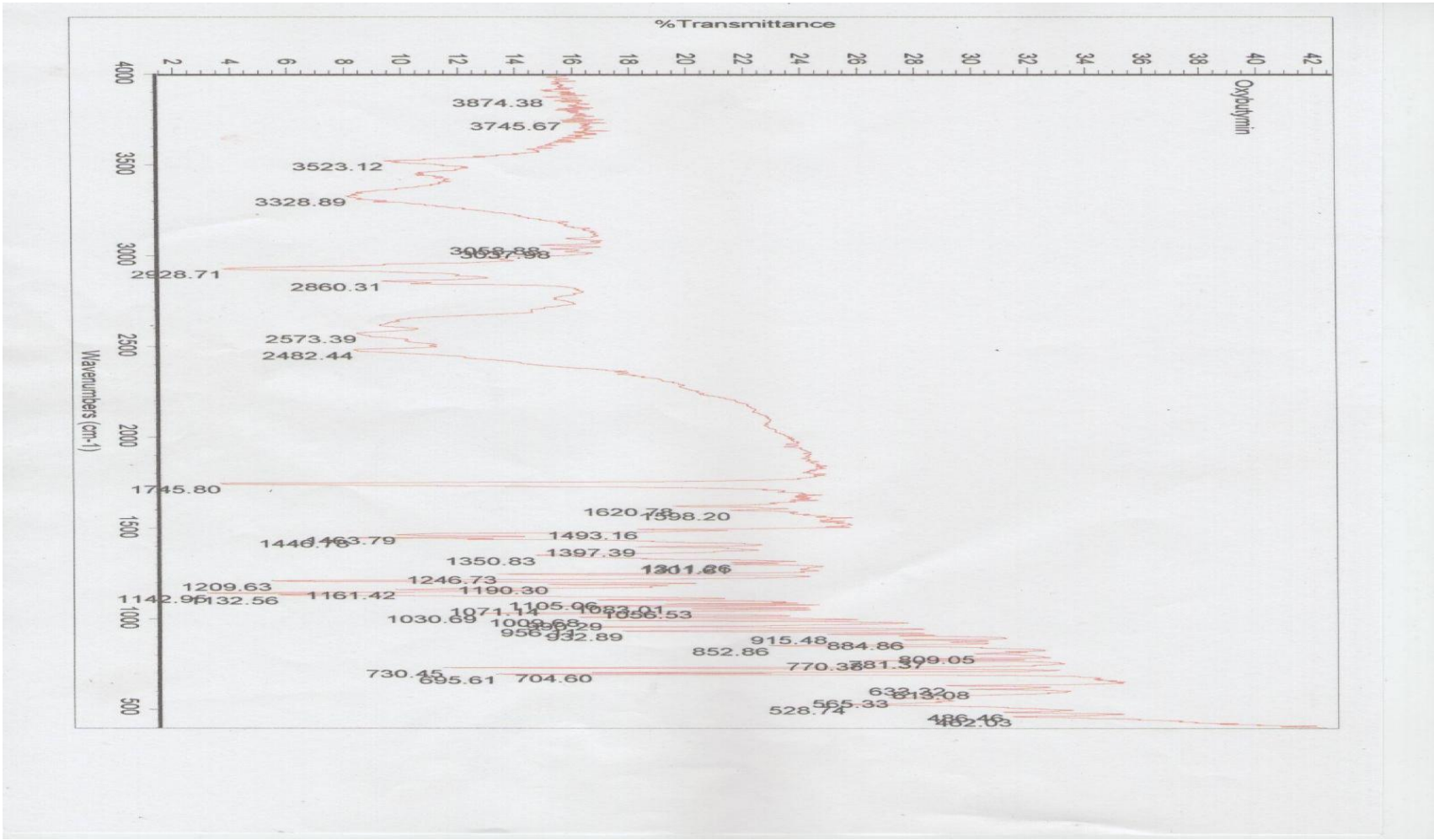


Fig : 9 FTIR Spectra of Oxybutynin Hydrochloride prepared formulation

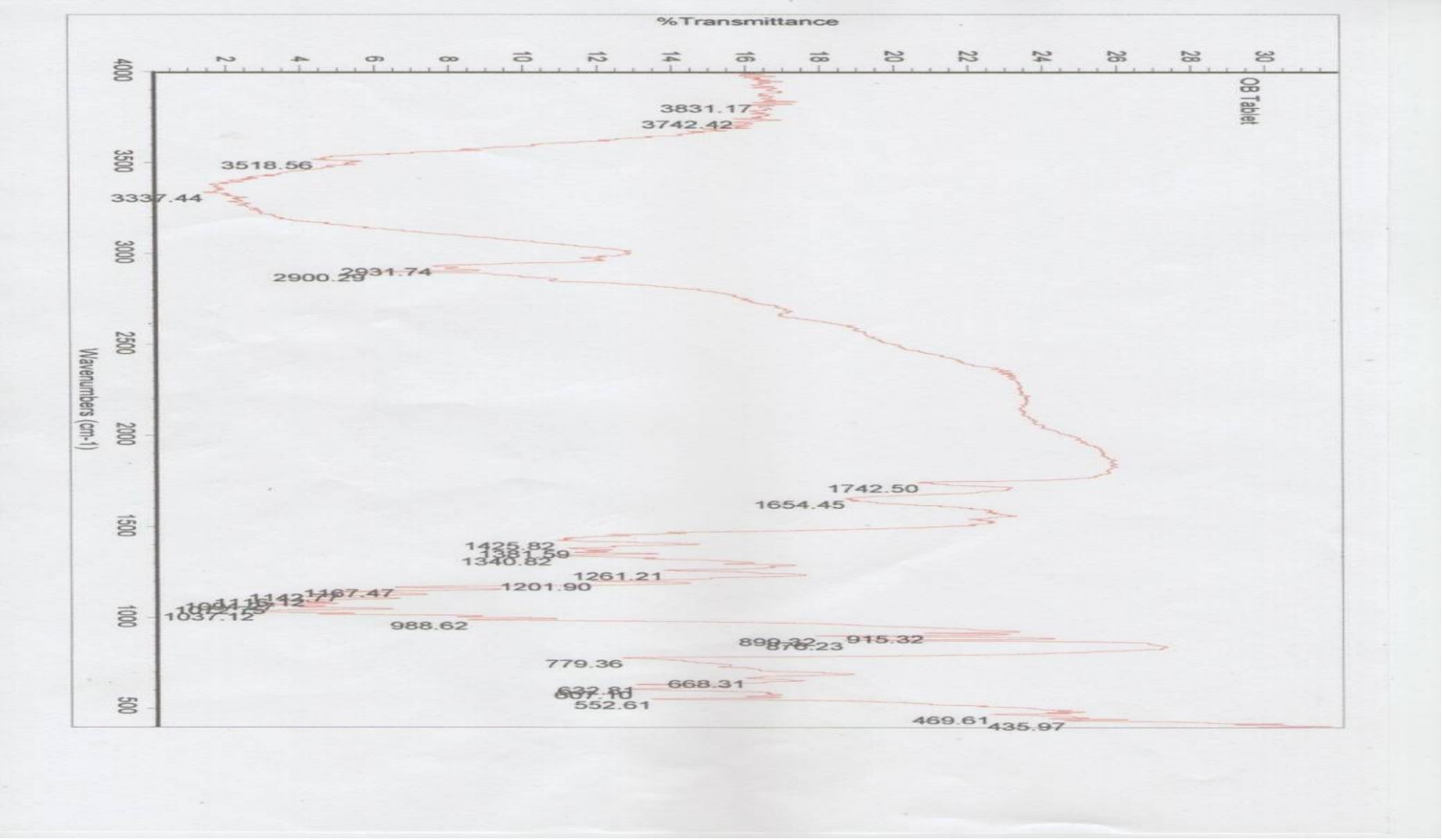


Fig: 10FTIR Spectra of Oxybutynin Hydrochloride pure drug.

Table: 20 Data for Standard plot of the Oxybutynin chloride using 6.8 pH Phosphate buffer

S.No	Concentration (µg/ml)	Absorbance (nm)
1	0	0.000
2	1	0.076
3	2	0.158
4	3	0.228
5	4	0.308

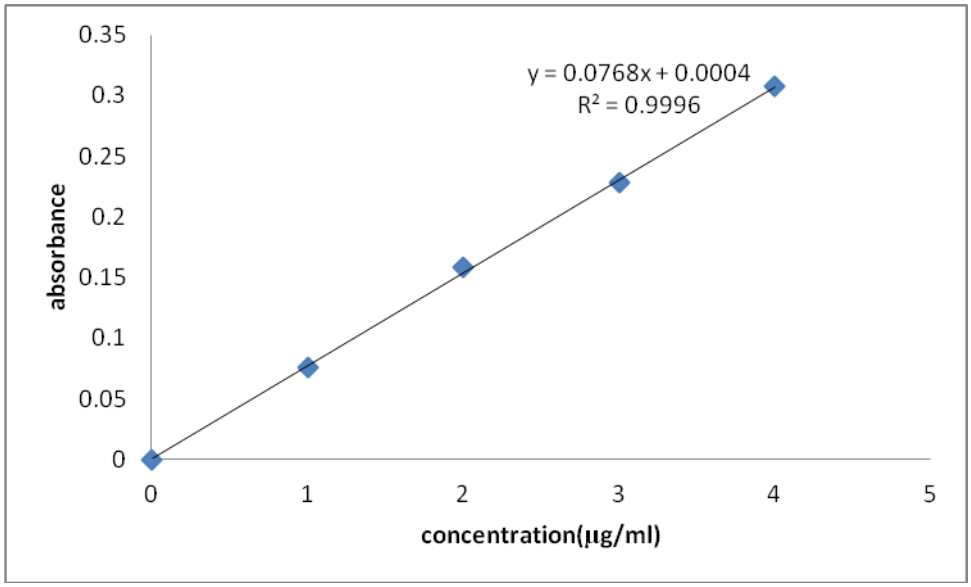


Fig: 11 Standard plot of the Oxybutynin Hydrochloride using using 6.8 pH Phosphate buffer at 210mn.

Table: 21 Data for Standard plot for Oxybutynin Hydrochloride using 0.1M HCl

S.No	Concentration (µg/ml)	Absorbance (nm)
1	0	0.000
2	1	0.082
3	2	0.166
4	3	0.248
5	4	0.339

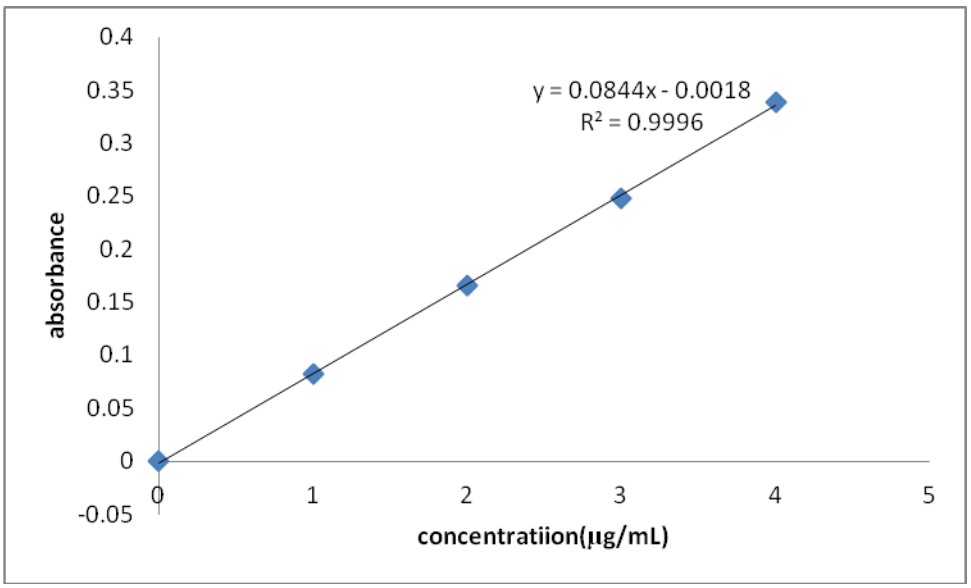


Fig: 12 Standard plot of Oxybutynin chlorideusing using 0.1N HCl at 210mn

Analysis of Ditropan (innovator) details:

With the help of analysis of the Ditropan we will able to compare the results obtained of our formulated product and it may helpful for calculation of the (f_2) similarity dissolution factor.

Analysis of the Ditropan was carried out for various physical parameters and In-vitro dissolution profile.

- Description.
- Thickness
- Weight Variation
- *in vitro* dissolution

Table: 22 Details of Ditropan

Generic name	**Oxybutynin Chloride Sodium**
Brand name	DitropanXL, Protonix
Manufactured and marketed by	Alza pharma
Strength	15 mg
Dosage form	Osmotic pump
Shape	Oval
Dimension	11.66 mm
Imprinting	'P 40' printed on one side
Average Weight	200- 206 mg
Storage Conditions	Store at 25° C excursions permitted (15-30°C) protect from moisture.

Determination of flow properties:

Table: 23 Formulation Parameters of formulated physical mixtures of drug and excipients.

Formulation	Blend Characterization			
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R
F1	0.69 ± 0.06	0.94 ± 0.012	26.59 ± 0.04	1.3 ± 0.04
F2	0.68 ± 0.07	0.84 ± 0.014	19.04 ± 0.04	1.32 ± 0.03
F3	0.582 ± 0.08	0.86 ± 0.010	20.93 ± 0.04	1.31 ± 0.06
F4	0.64 ± 0.06	0.79 ± 0.014	18.98 ± 0 .06	1.27 ± 0.04
F5	0.57 ± 0.08	0.78 ± 0.012	16.66 ± 0.04	1.29 ± 0.08
F6	0.59 ± 0.08	0.80 ± 0.014	20.00 ± 0.04	1.35 ± 0.06
F7	0.571 ± 0.04	0.785±0.012	27.27 ± 0.06	1.35 ± 0.08
F8	0.587 ± 0.04	0.792±0.012	19.883 ± 0.02	1.34 ± 0.04
F9	0.584 ± 0.02	0.781±0.014	20.224 ± 0.03	1.33 ± 0.04

Table: 24 Various Physical Properties of Oxybutynin Hydrochloride core Tablets

Formulations	Weight variation	Hardnes	Thicknes	Friability	%drug content
F1	200 ±0.56	8.4±0.12	4.42±0.016	0.21±.008	102.3
F2	200 ±0.65	10.5±0.14	4.43 ±0.012	0.160±0.06	103
F3	200 ± 0.58	11.7±0.12	4.45±0.015	0.015±0.008	98
F4	200 ± 0.62	13.6±0.16	4.47 ± 0.013	0.014±0.04	100.6
F5	200 ± 0.35	13.7±0.14	4.43 ± 0.014	0.018±0.005	101.7
F6	200 ± 0.68	13.8±0.15	4.42 ± 0.012	0.021±0.07	104.6
F7	200 ±0.65	12.6±0.15	4.47 ± 0.015	0.010±0.09	101.7
F8	200 ± 0.50	13.0±0.16	4.46 ± 0.014	0.018±0.008	102.1
F9	200 ± 0.54	13.6±0.13	4.46 ± 0.016	0.0170±0.007	104.6

Table: 25 Physical Properties of Oxybutynin Hydrochloride Enteric coated Tablets:

Formulations	Weight variation
F1	204.73 ± 0.25
F2	205.61 ± 0.45
F3	204.72 ± 0.29
F4	203.71 ± 0.69
F5	205.12 ± 0.79
F6	204.09 ± 0.85
F7	205.18 ± 0.55
F8	204.21 ± 0.65
F9	205.65 ± 0.30

Table: 26 Acid resistance test for Oxybutynin Hydrochloride ER Tablets For 2 hours in 0.1M HCl

S.No	%Enteric coating	Dissolution in 0.1N Hcl	Remarks
F1.	2.25	Fail	Tablet opened
F2.	2.25	Fail	Tablet opened
F3.	2.25	Fail	Tablet opened
F4.	4.5	Pass	Tablet remain intact
F5.	4.5	Pass	Tablet remain intact
F6.	4.5	Pass	Tablet remain intact
F7.	4.5	Pass	Tablet remain intact
F8.	4.5	Pass	Tablet remain intact
F9	4.5	Pass	Tablet remain intact

***In vitro* dissolution Studies:**

Table: 27 *in vitro* dissolution profile for the Ditropan .

Percentage cumulative drug release								
Time (hrs)	**limits**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	7	4	5	5	5	5±0.98
4	10-30%	24	27	25	26	24	23	24±1.47
8	35-65%	47	49	48	47	45	47	47±1.32
12		70	71	69	68	65	69	68±2.06
16	NLT-75%	81	79	78	75	78	79	79±1.96
24		97	96	95	94	96	94	95±1.21

n = 6

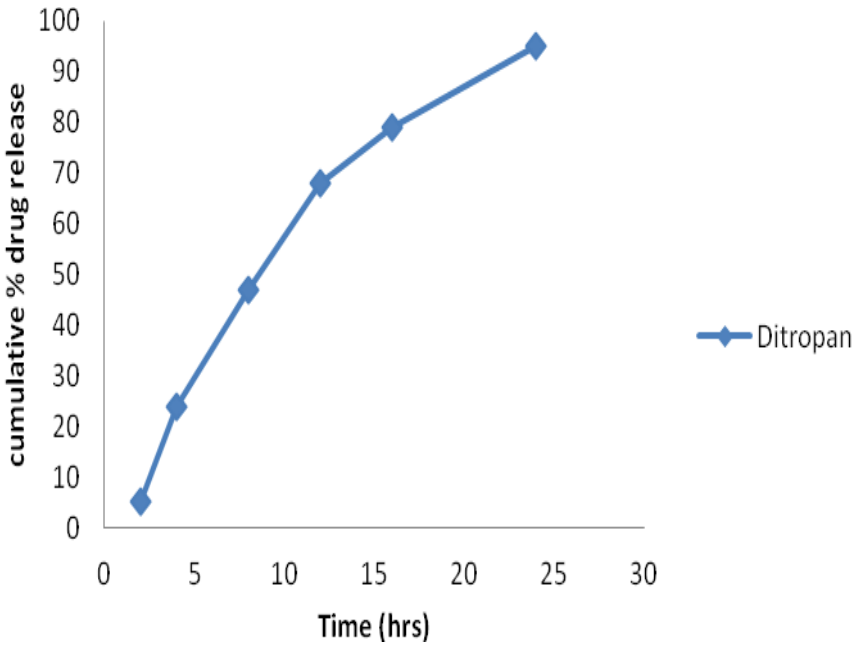


Fig: 13 *In vitro* dissolution profile for the Ditropan.

Table: 28 Comparative *in vitro* dissolution profiles for the formulation F1 with Ditropan.

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	1	2	1	1	1	2	1.57±0.5
4	10-30%	24	8	9	8	9	9	7	8.33±0.8
8	35-65%	47	15	16	14	12	17	12	13.66±2
12		68	23	21	23	22	26	21	23±1.86
16	NLT-75%	79	54	52	54	52	55	52	53.16±13
24		95	73	71	73	74	75	72	72±1.4

n = 6

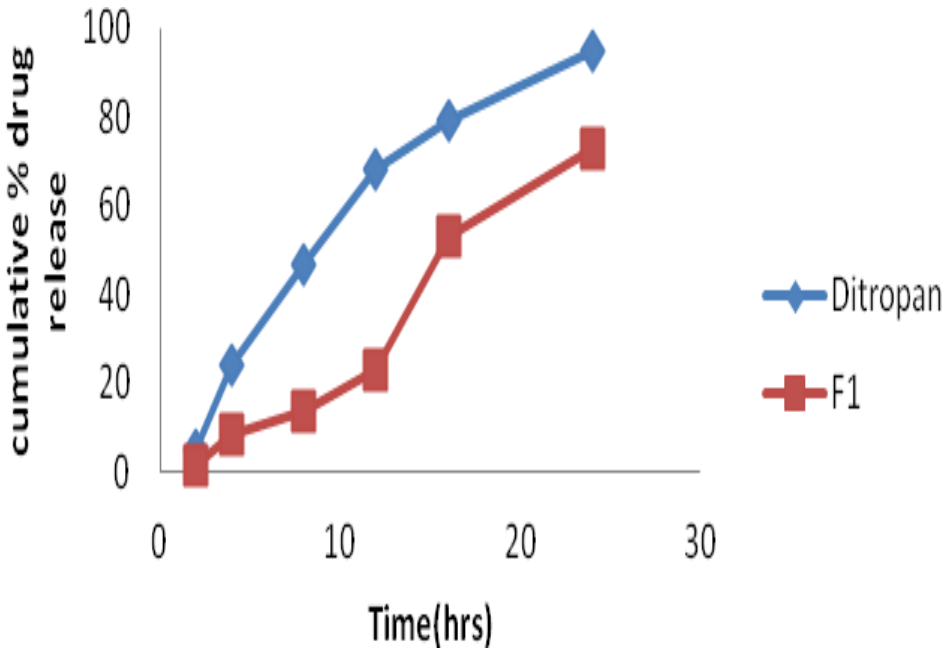


Fig: 14 Comparative *in vitro* dissolution profile for the formulation F1 with Ditropan

Table: 29 Comparative *in vitro* dissolution profile of F2 with Ditropan.

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	1	2	1	3	2	4	2.1±1.6
4	10-30%	24	10	9	12	13	11	10	11±1.3
8	35-65%	47	24	22	25	26	20	22	23±2.0
12		68	33	31	33	32	31	34	32.3±1.1
16	NLT75%	79	58	57	53	60	61	57	59±2.6
24		95	77	78	76	80	79	81	79.5±1.7

n = 6

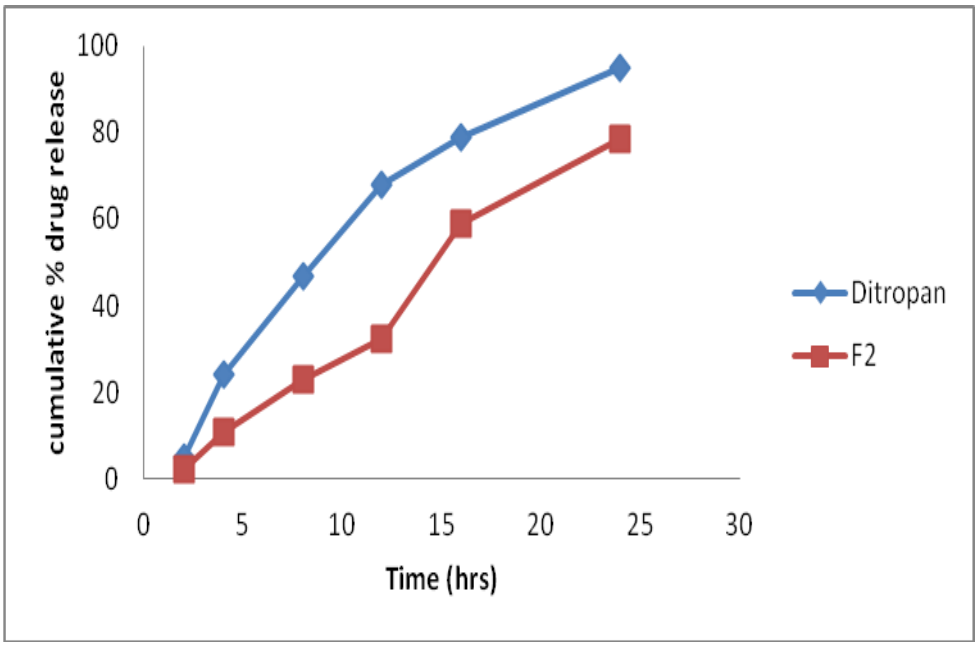


Fig: 15 Comparative *in vitro* dissolution profile of F2 with Ditropan

Table: 30 Comparative *in vitro* dissolution profiles for the formulation F3 with Ditropan

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	1	2	1	1	2	2	1.57±0.5
4	10-30%	24	9	7	10	9	7	8	8.12±1.10
8	35-65%	47	21	24	23	21	22	21	22.14±1.15
12		68	33	31	33	32	31	32	32±0.81
16	NLT-75%	79	54	55	53	56	50	52	53.33±1.97
24		95	77	72	74	72	71	73	73.16±1.95

n = 6

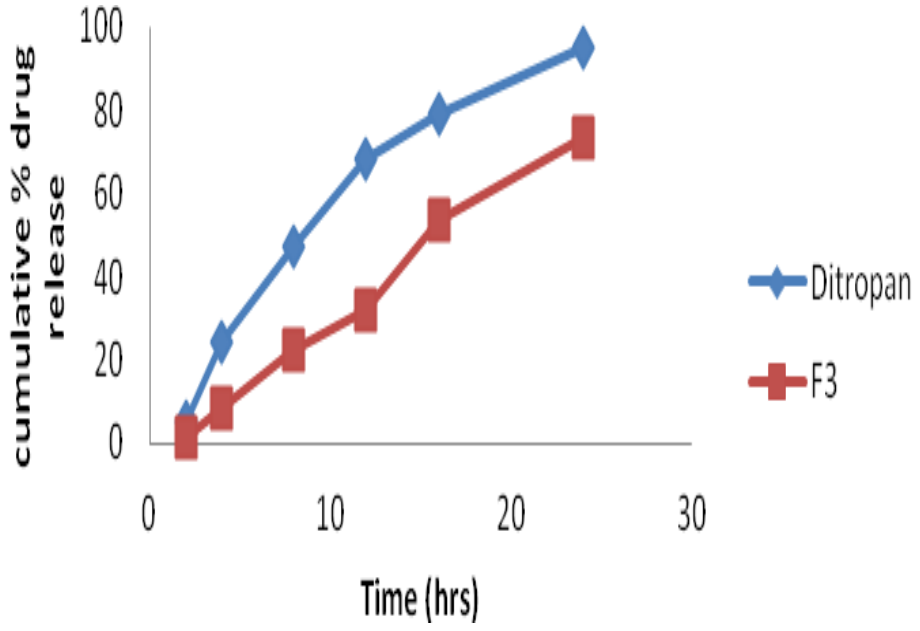


Fig: 16 Comparative *in vitro* dissolution profile of F2 with Ditropan

Table: 31 Comparative *in vitro* dissolution profile for the formulation F4 with Ditropan

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	3	**2**	1	**1**	**2**	**2**	2±0.69
4	10-30%	24	13	10	11	12	13	9	11.2±1.49
8	35-65%	47	26	24	24	25	22	27	26±1.67
12		68	33	31	33	32	31	32	37.71±2.3
16	NLT-75%	79	58	59	60	60	57	57	57.83±1.2
24		95	81	76	80	78	79	77	78.5±2.5

n = 6

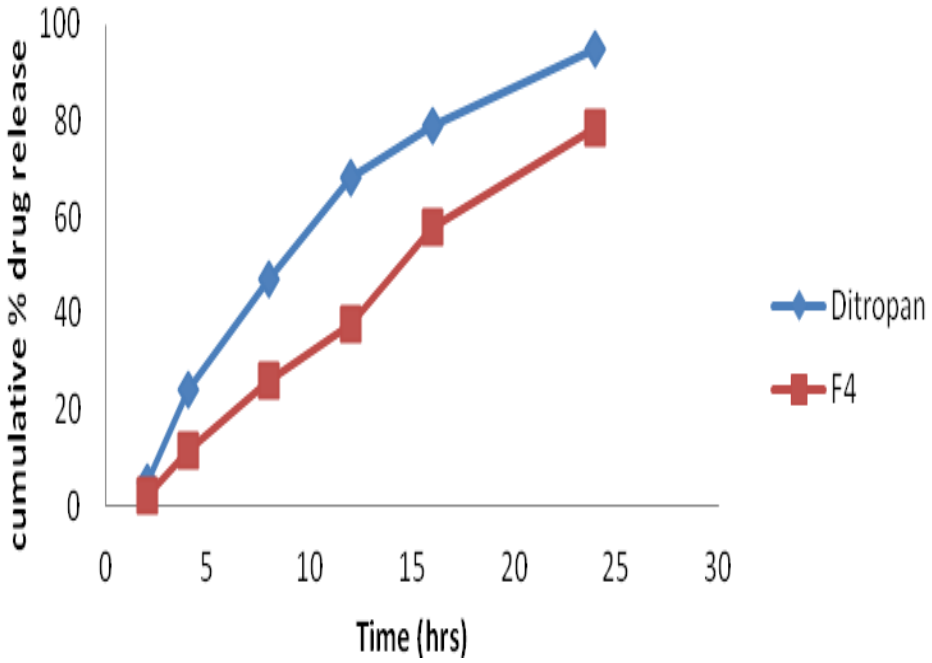


Fig: 17 Comparative *in vitro* dissolution profile for the formulation F4 with Ditropan

Table: 32 **Comparative *in vitro* dissolution profiles for the formulation F5 with Ditropan**

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	3	2	3	2	4	2	2.71±0.74
4	10-30%	24	15	16	17	16	19	16	16.5±1.25
8	35-65%	47	31	36	34	33	34	36	34±1.73
12		68	46	50	49	46	47	48	47.66±1.49
16	NLT75%	79	62	64	65	65	65	65	64.3±1.10
24		95	81	79	81	83	84	83	81.83±1.67

n = 6

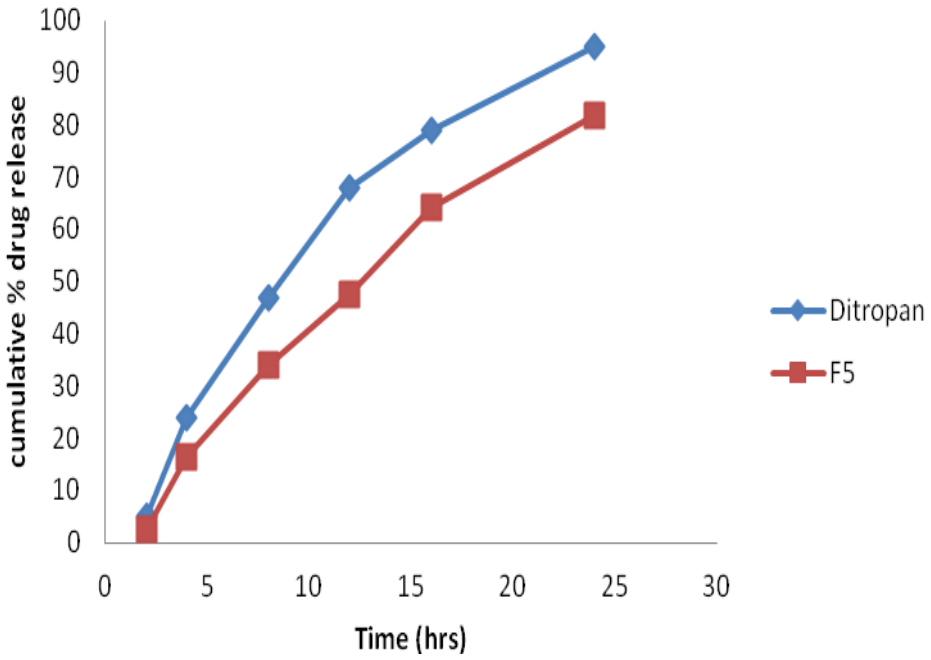


Fig:18 **Comparative *in vitro* dissolution profile for the formulation F5 with Ditropan**

Table: 33 Comparative *in vitro* dissolution profile for the formulation F6 with Ditropan

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	5	3	3	4	4	5	3.87±0.81
4	10-30%	24	20	22	23	24	23	22	20.74±1.38
8	35-65%	47	47	45	46	47	44	45	45.66±1.10
12		68	60	63	64	62	59	62	61.6±1.69
16	NLT-75%	79	72	70	72	73	74	74	72.6±1.38
24		95	89	91	90	94	93	92	91.5±1.70

n = 6

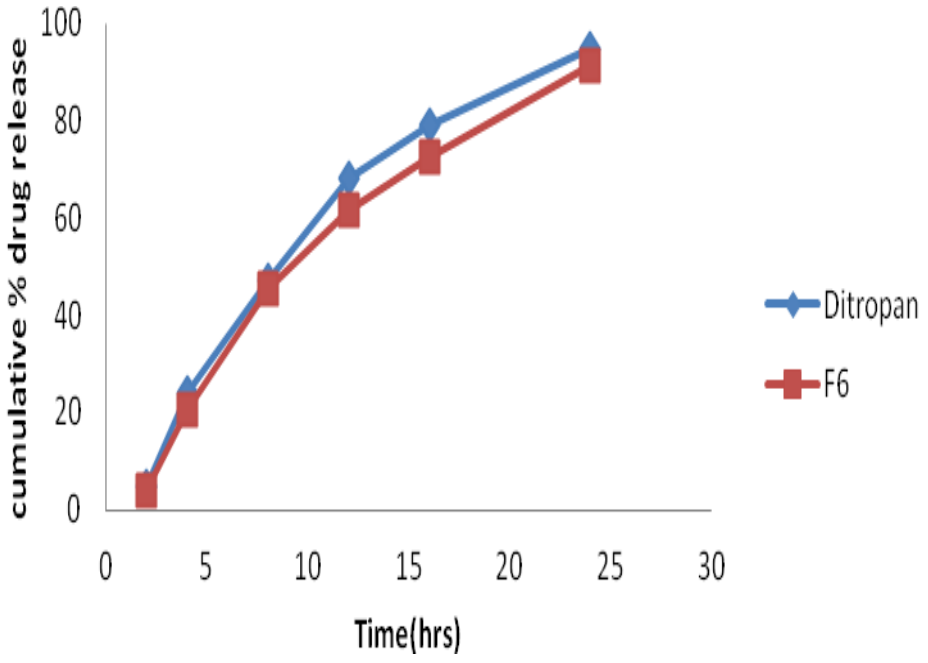


Fig:19 Comparative *in vitro* dissolution profile for the formulation F6 with Ditropan

Table: 34 Comparative *in vitro* dissolution profile for the formulation F7 with Ditropan

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	5	3	3	4	4	5	4±0.816
4	10-30%	24	24	27	27	26	24	25	25.5±1.25
8	35-65%	47	47	49	48	47	47	47	47.5±0.76
12		68	70	69	67	65	68	71	68.3±1.97
16	NLT-75%	79	75	74	73	69	71	74	74±2.11
24		95	94	90	89	89	93	94	92±2.22

n = 6

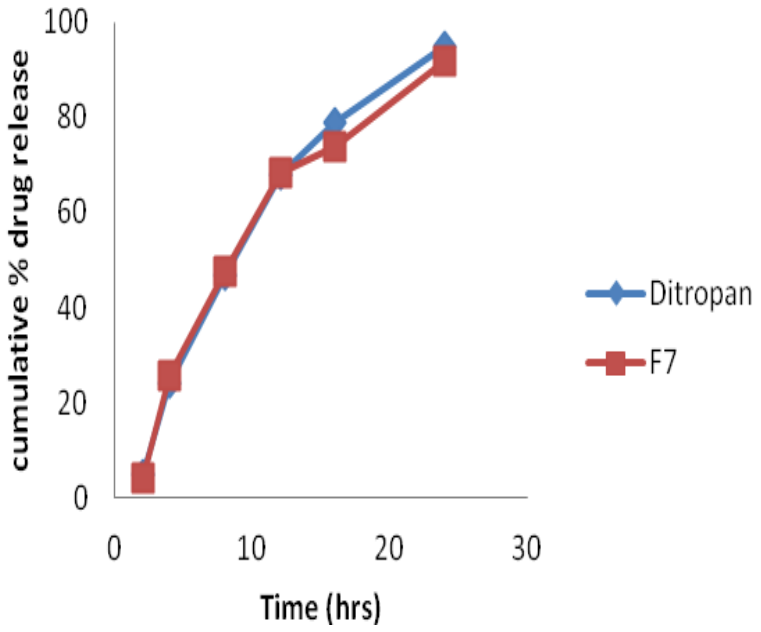


Fig: 20 Comparative *in vitro* dissolution profile for the formulation F7 with Ditropan

Table: 35 Comparative *in vitro* dissolution profile for the formulation F8 with Ditropan

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	4	**7**	6	**7**	**6**	**7**	6.8±1.09
4	10-30%	24	26	27	28	26	27	25	26±0.97
8	35-65%	47	47	49	48	47	47	47	49±0.95
12		68	69	70	67	65	69	68	67±1.67
16	NLT-75%	79	75	74	73	69	74	71	77±2.6
24		95	94	97	95	96	97	98	96.1±1.34

n = 6

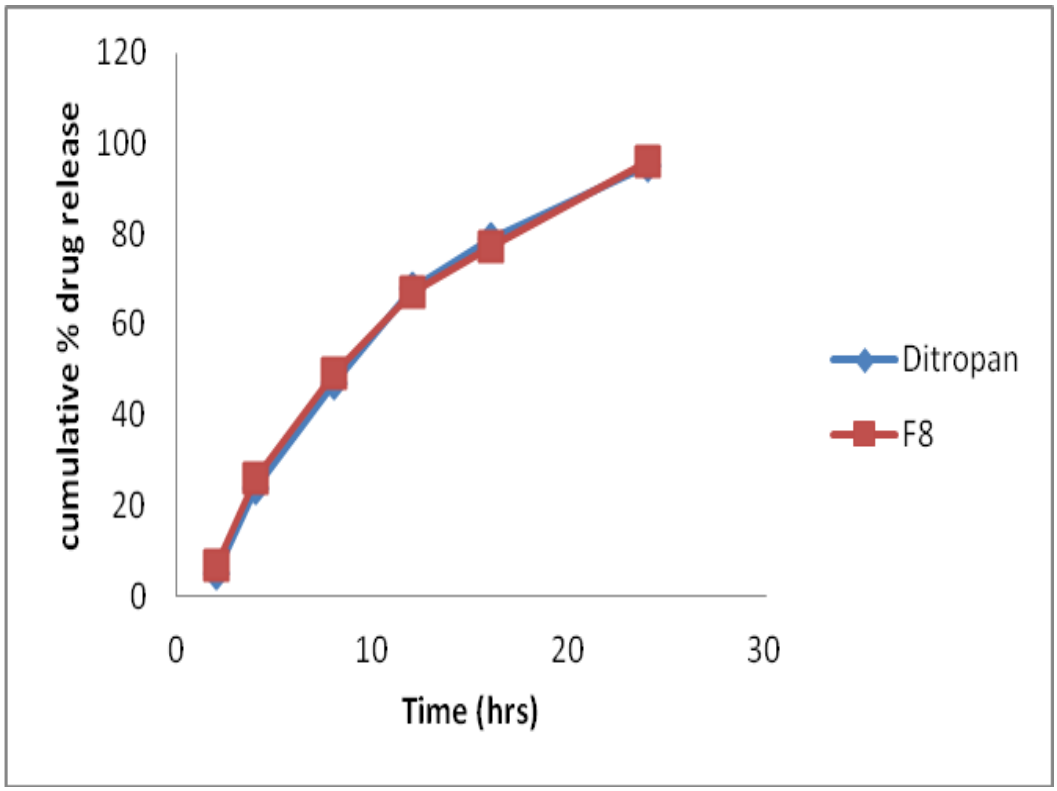


Fig: 21 Comparative *in vitro* dissolution profile for the formulation F8 with Ditropan

Table:36 Comparative *in vitro* dissolution profile for the formulation F9 with Ditropan

Percentage cumulative drug release									
Time (hrs)	**limits**	**Ref**	**Unit 1**	**Unit 2**	**Unit 3**	**Unit 4**	**Unit 5**	**Unit 6**	**Average**
2	0-10%	5	5	7	6	7	5	5	5.75±0.89
4	10-30%	24	24	27	27	26	24	25	25.5±1.25
8	35-65%	47	47	49	48	47	47	47	47.5±0.76
12		68	70	69	67	65	68	71	68.3±1.97
16	NLT75%	79	75	74	73	69	71	74	76±2.41
24		95	94	96	95	94	97	95	96±1.11

n = 6

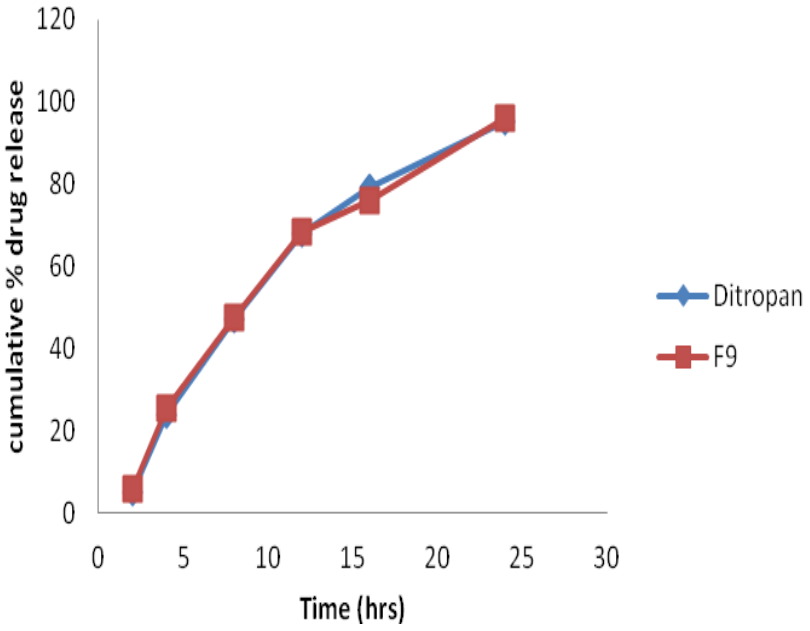


Fig: 22 Comparative *in vitro* dissolution profile for the formulation F9 with Ditropan

Determination of release kinetics

Table: 37 kinetic studies of matrix Tablets

Release kinetics	R^2	Intercept	slope
Zero order	0.934	10.49	3.29
First order	0.953	4.964	-0.14
Higuchi	0.934	11.0	25.61
Korsmeyer peppas	0.991	0.66	0.74

Dissolution- Zero Order kinetics

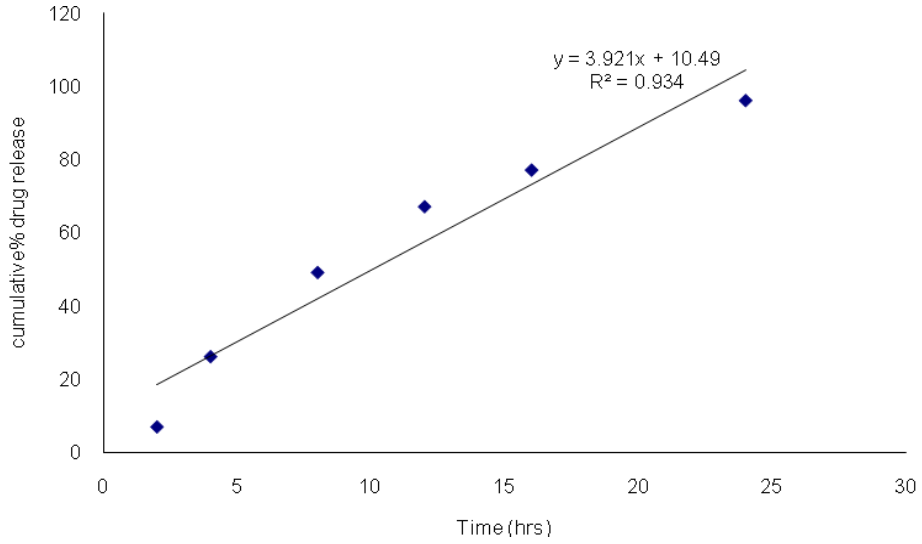


Fig: 23 Graph for the formulation F8-Zero Order Kinetics

Dissolution- First order Kinetis

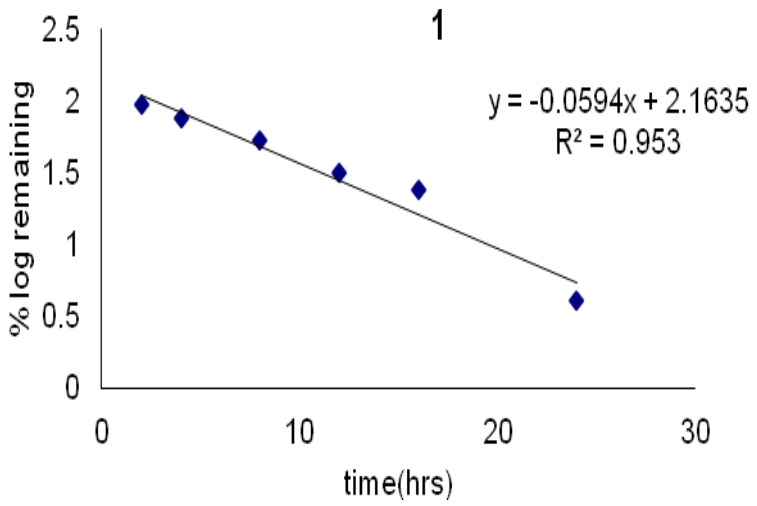


Fig: 24 Graph for the formulation F8-First Order Kinetics

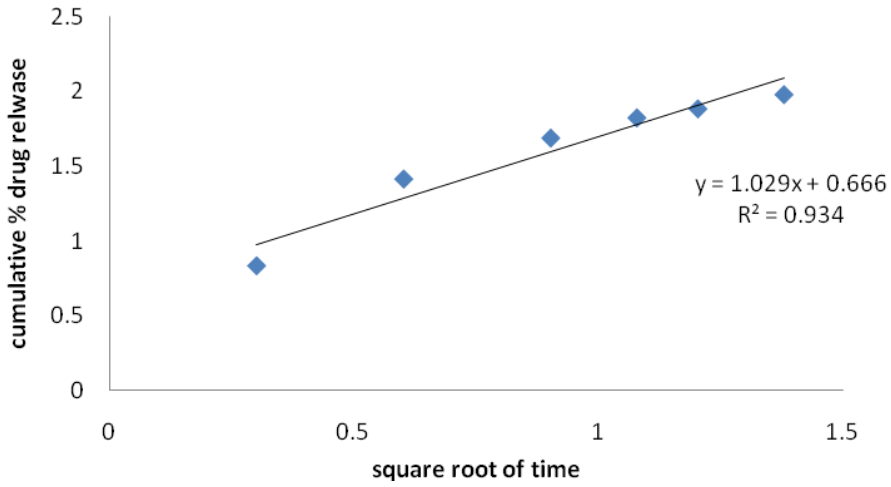


Fig 25: Graph for the formulation F8-Higuchi model

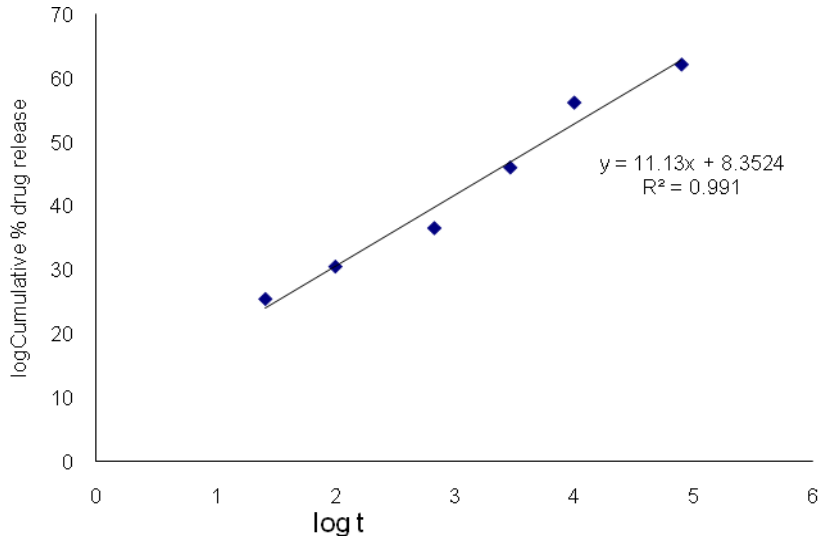


Fig: 26 Graph for the formulation F8- Kors meyer Peppas model

Difference Factor *(f1)* & Similarity Factor (*f2*) Calculation

Table: 38 Difference Factor *(f1)* & Similarity Factor (*f2*)

Difference Factor (*f1)* & Similarity Factor (*f2*)					
Time (t) [in Hours]	**Ditropan ®**	**Test (T)**	**Rt-Tt**	**$(Rt-Tt)^2$**	**|Rt-Tt|**
2	5	6.8	-1.80	3.24	1.80
4	24	26	-2.00	4.00	2.00
8	47	49	-2.00	4.00	2.00
12	68	67	1.00	1.00	1.00
16	79	77	2.00	4.00	2.00
24	95	96.17	-1.17	1.37	1.17
Sum	**318.00**			**17.61**	**9.97**
Number of Time points or intervals (Excluding Zero)					**6**
Difference Factor - F1 [Acceptance Criteria : 0 - 15]					**3.14**
Similarity Factor - F2 [Acceptance Criteria : 50 - 100]					**85.13**

Stability Studies:

Table: 39 Results for stability studies

S.No.	Tests	Initial	1 Month
1.	**Thickness (mm) ± SD**	4.5 ± 0.01	4.4 ± 0.11
2.	**Diameter (mm) ± SD**	4.2±0.02	4.2±0.03
3.	**Hardness (kg/cm^2) ± SD**	12.2 ± 0.01	12.1 ± 0.1
4.	**Friability (% W/W) ± SD**	0	0
5.	**Weight variation (%) ± SD**	1.1 ± 0.12	1.0 ±0.3
6.	**Drug content (% ± SD**	99.50 ±.02	99.20 ± 0.03

The Stability studies on optimized formulation of Oxtbutynin hydrochloride extended release tablets were conducted according to the ICH guidelines. The various parameters tested during during studies of Oxtbutynin Hydrochloride extended release tablets are show in table. The formulation were withdrawn at suitable intervals (initial and 1 month) and analysed visually for physical appearance and evaluated for different tests. The tablets showed no visual differences and compiled with description. The percentage of drug release from the formulation F8 at different intervals of time is given in **Table: 39** and was found to be matching with specification. From the above results, it can be concluded that the formulation F8 of Oxtbutynin Hydrochloride extended release tablets are stable.

Chapter 8

Discussion

Discussion

8.1 Preformulation :

The experimental work started with the raw material analysis of Oxybutynin hydrochloride as per USP, the physical properties such as bulk density the tapped density, Carr's index, Hausner's ratio and angle of repose values were depicted in the **Table: 17**

8.2 Drug Excipient- compatibility study:

The physical compatibility test between drug and excipients were carried out at 40º C ± 2 ºC/75 ± 5 % RH for 15 days and 30 days. The mixture does not show any visible change, thus indicating drug and other excipients do not have any physical incompatibility.

Fig: 9 Shows the FTIR spectra of plain Oxybutynin Hydrochloride and the Oxybutynin Hydrochloride formulation.

The FTIR spectra of pure Oxybutynin Hydrochloride showed major band at 3328.89 cm^{-1} for –OH stretch 1745cm^{-1} for C=O stretch, and 2928.71 cm^{-1} for CH_2 asymmetrical/symmetrical stretch. The Oxybutynin Hydrochloride in the physical mixture showed the major–band at 3337.4 cm^{-1} for OH stretching and 1742.50 cm^{-1} for C=O and 239 or 1.74 for CH_2.

IR spectra of drug and excipients physical mixture shown in **Fig: 10** also revealed that no considerable change was observed in bands of oxybutynin hydrochloride. Hence it indicates that the absence of interaction between the oxybutynin Hydrochloride and the polymer and excipients used in the formulation.

Standard calibration curve of oxybutynin hydrochloride in pH6.8 phosphate buffer and 0.1 M HCl were derived from the concentration, and corresponding absorbance values. Linear regression analysis gave the equations for the line of best fit as Y =0.0765X, $R^{2=}$0.9997 and Y=0.0884X, $R^{2=}$0.9996

respectively. Linearity was observed in concentrations between1 to 5µg/ml.

8.3 Preparation of Matrix tablet

Oxybutynin Hydrochloride is an anticholinergic which is used for the treatment of urinary incontinence. Because of its short half life attempts have been made to develop an extended release formulation to reduce the dosing frequency. HPMC K 100 M**,** a hydrophilic polymer with high viscosity, which when comes in contact with aqueous solutions hydrate and swells and forms a hydrogel matrix. Thus matrix formulation upon contact with gastric fluids swells and retards the release of Oxybutynin from the matrix. Pharmatose 200M and Avicel 102 were used as tablet diluents and their effect on the drug release was studied.

Eudragit L30D55 was used as enteric coating polymer which dissolves as pH above 5.5 to prevent the drug from degradation in the gastric pH. Different concentrations of EudragitL30D55 were studied.

8.4 Evaluation of tablets

Bulk density, Tapped density, Carr's index, & Hausner's ratio were evaluated for the prepared blend, and the results showed in the **Table**: **23** indicate good flow property and compressibility. The physical parameters for core and enteric coated tablets like weight variation, thickness, hardness were evaluated. For core tablets the results were shown on **Table: 24.**

8.4.1 Effect of HPMC K100M on drug release

in vitro dissolution study of the formulations F1& F2 containing 40% and 35% of HPMC K 100M were prepared by direct compression method and compared, the flow of the blend from the hopper was not good and also the release from the formulations F1 & F2 were found to be 72% & 79% at the end of 24^{th} hour, which shows the release was not within the USP specified limit. A trail using Kollidon K 90 F with different concentrations (2.5% and 10%) in combination with HPMC K100M for formulations F3 and F4, was done but the granules formed were very

fine and during compression spillage from the lower punch was observed and the release from the formulations at the end of 24th hour was found to be 73% and 78% which are not complying with the specified limits. The release profiles for **formulations were shown on Table: 30 &31, and fig: 16& 17.**

Hence to meet the required release profile Oxybutynin hydrochloride, HPMC K100M , used alone to retard the release of the drug from the matrix formulation. Different prototypes F5, F6, F7 & F8 were developed using different concentrations of polymer (30%, 25%, 22.5% & 20%) respectively. The release from the formulation F8 containing 20% HPMC K 100M at 2nd, 4th, 8th, 12th, 16th,and 24th hrs was found to be 6.8%,26%,49%,67%,77% and 96% respectively. At the end of 24th hour which is similar to that of similar to that of Ditropan.

When the concentration of the HPMC K 100M increased, the drug release was found to be decreased. Therefore, from formulations F1 to F8 different concentration of HPMC K100M showed different release profiles, of these formulations F8 observed to be followed USP specifications for extended release tablets. However, in order to confirm the effect of HPMC K100M on Oxybutynin Hydrochloride release, formulation F10 was prepared with 18% HPMC k100M(not shown in the formulation table),but the release was found higher (93%) at end of 16th hour. Therefore the polymer concentration optimized to be 20 % (F8).

8.5 Acid resistance test:

Acid resistance test was performed to optimize the concentration of enteric coating polymer. Formulations F1, F2, and F3 coated with 4.5 mg were failed in the acid conditions and they have opened the layer in the Acid stage only. Hence, concentration of enteric coating was increased to 9 mg from formulations F4. The formulations remain intact in the acidic stage and opened only after entering alkaline pH only. The values for acid resistance were depicted in the **Table: 26.**

8.6 Release kinetic study for optimized matrix tablet:

The plot of cumulative percentage drug release as a function of time indicates that none of the formulation follows zero order or Higuchi Kinetics **(Table: 37)** the line of best fit obtained was first order release kinetics (R^2 =0.956) and Korsmeyers Peppas model, the drug release data further analysed for curve fitting and the results (n=0.74) confirmed that the formulation followed non-Fickan (Anamalous) diffusion kinetics.

8.7 Reproducibility batch

To check the reproducibility of batch, another batch of F9 was prepared with the same formula of F8. The drug release at drug release at 2^{nd}, 4^{th}, 8^{th}, 12^{th}, 16^{th}, and 24^{th} hrs was found to be 5.75%, 25.5%, 47.5%, 68.3%, 76% and 96% respectively, for Oxybutynin hydrochloride. Hence the drug release from reproducibility batch (F9) was observed similar to that of optimized formulation. The results were shown in the **Table: 36** & **fig: 22.**

8.8 Comparision between optimized batch and Ditropan XL

The optimized batch (F8) was compared with the Ditropan. The drug release of optimized batch and the market product was found to be 96% and 95% at the end of 24^{th} hour. **Table: 37** shows the formulation F-8 was seemed to be close to the Ditropan's release profile. Then similarity factor (f_2) was calculated between formulation F-8 and Ditropan. Similarity factor was (85.13); therefore, formulation F-8 has similar release profile to the marketed formulation release.

8.9 Stability batch

Stability studies were conducted for the formulations F8 and F9. The stability study was performed at 40°C /75 % RH for a specific time period. The tablets were analysed for appearance, weight variation, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at the above mentioned. Storage conditions the results were depicted in **Table: 39**

Chapter 9

Summary

Summary

Chapter I begins with a general introduction presenting an overview of about extended release drug delivery systems.in the part of introduction the advantages, disadvantages, mechanism of extended release systems and matrix tablets were discussed thoroughly.

Existing literature reviewed in the **chapter-II** the review of literature carried out for selected drugs, polymer and design and evaluation of matrix tablets.

Chapter-III gives information on the selection of drugs and excipients, there by Oxybutynin hydrochloride is suitable candidate for extended release dosage form.

Chapter IV deals with the methodology followed for the preparation of matrix tablet after the raw material analysis and the Drug:excipient compatibility study. Ion for the preparation and evaluation of extended release matrix tablets of Oxybutynin hydrochloride.

Chapter V Includes the results of all the formulations .the drug excipient compatability study was done and found to have no interactions between oxybutynin hydrochloride and excipients, all the qualitative and quantative parameters were analyzed and tabulated. The plot of time versus percentage of drug was release was also given after the table the brief description about table and graph were also given for all formulations.

Precompressional parameters of matrix tablets (bulk density, tapped density, Carr's, index Hausner's ratio and angle of repose) are in the range of official standard, indicated that granules prepared by wet granulation method. The post compressional parameters of extended release tablets (hardness, friability, weight variation, thickness, and drug content), were with in the limits.

in vitro dissolution profile of Extended release matrix tablets containing oxybutynin Hydrichloride from the formulation F8, drug release at 2^{nd}, 4^{th}, 8^{th}, 12^{th}, 16^{th} and 24^{th} hrs was found to be 6.8%, 26%, 49%, 67%, 77% and 96% respectively.

The kinetic of drug release for formulation F8 was calculated and plotted. The formulation F8 follows first order release kinetics and the drug release mechanism was found to be non-Fickan anomalous diffusion.

The optimized formulation was compared with marketed product and showed similar release profile.

Stabalitiy studies were conducted for the formulations F8 and F9.The stability study was performed at $40^{\circ}C$ /75 % RH for a specific time period. The tablets were analysed for appearance, weight variation, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at the above mentioned Storage conditions.

Chapter 10

Conclusion

Conclusion

The oral extended release matrix tablet containing 15mg of Oxubutynin Hydrochloride provided extended release for 24 hours. The hydrophilic polymer HPMC K100M alone gave a satisfied release profile compared in combination with Kollidon K90 F. The optimized formulation followed first order kinetics while the drug release mechanism was non-Fickan (Anomalous type) controlled by diffusion through swollen matrix.

The optimized formulation F8 and the marketed formulation (Ditropan) were found to have a similar *in vitro* release profile, which is confirmed by f_1 and f_2 values.

A month of stability study data revealed no marked changes in the physical parameters and drug release profile.

Chapter 11

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